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ACIDOSIS OCCURRING WITH DIARRHEA *

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During the course of attacks of severe diarrhea, not of the ileocolitis type, in infants, alterations in the respiration are not infrequently encountered. The usual abdominal type of respiration of the young child is succeeded by one which is both costal and abdominal. The most striking feature is the amplitude of the respirations and the distinct effort with which they are accomplished. They are heaving, the thorax being often greatly elevated and depressed and the accessory muscles of respiration brought into play. There is no evidence of obstruction and no cyanosis. The frequency of the respiration is usually increased but not greatly so. Sometimes there is a greater or less alteration of the depth of the individual respirations so that a modified Cheyne-Stokes type results, but in general the excursions of the thorax and abdomen are nearly the same with succeeding respirations. This increased pulmonary ventilation or hyperpnea may go on uninterruptedly for many hours. Eventually, in fatal cases, the respirations become feebler and feebler with only occasional deep gasps, and finally they cease altogether. It is as if the respiratory center were exhausted by the exertions which it has undergone.

Czerny[1] was, we believe, the first to describe this alteration in the character of the respiration in nutritional conditions. He called attention to the resemblance between the respiration of infants dying of gastro-intestinal disease and that of rabbits poisoned with mineral acids.

The object of the present communication is to give in some detail observations which have enabled us to demonstrate that the hyperpnea in many cases of severe diarrhea[2] is associated with, and dependent on, the presence of acidosis.

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* Submitted for publication, March 15, 1916.

* From the Harriet Lane Home and the Department of Pediatrics of the Johns Hopkins University.

1. Czerny: Jahrb. f. Kinderh., 1897, xlv, 271.

2. Preliminary reports on this subject have been made in the Proceedings of the Society for Experimental Biology and Medicine, 1914, xii, 51, and in The Bulletin of the Johns Hopkins Hospital, 1916, xxvii, 63.

The term "acidosis" has been used in connection with nutritional disorders ever since it was first shown by Keller[3] that in such disorders there is to be found at times a great increase of the ammonia coefficient (ammonia nitrogen to total nitrogen). Using a very inexact method (Schlösing's), he determined that the ammonia coefficient of infants varied between 2 and 57 per cent. With Czerny, Keller[4] pointed out that an increase of fat in the food produced in some patients a rapid and marked increase of the actual and relative amount of ammonia excreted in the urine. Numerous observers have substantiated these findings. It has been sufficiently shown, however, that even a very marked amount of fat may not produce such a change. Thus Howland and Cooke[5] fed to an infant of 10 months a diluted cream mixture containing about 7 per cent. fat. The amount of fat ingested each day was 76 gm. With this food there was no increase of ammonia. In two other children there was no increase of ammonia excretion until marked diarrhea occurred. Such has been the experience also of others. Amberg and Morrill[6] have shown that in a normal infant an increase of fat in the food is without effect on the ammonia coefficient if the amount of protein remains constant. Czerny and Keller[4] insisted on the dependence of increased ammonia excretion on the condition of the child; it occurred when there was evidence of gastro-intestinal disturbance. It is with the presence of diarrhea chiefly that the ammonia coefficient is increased. This has been a very general, almost a regular, finding.

To account for the excess of ammonia, Keller looked for abnormal acids but was not able to prove their presence. Steinitz[7] determined a mineral loss by the intestine and believed that it was the mineral loss (especially the loss of sodium) that made necessary an increase of ammonia to compensate for the deficiency of bases in the blood and tissues. This acidosis was, therefore, to be considered as relative, inasmuch as it was not due to excessive acid production.

While this increase of ammonia, due to whatever cause, has been spoken of as acidosis, the acidosis has not usually been considered an important or threatening condition. Steinitz emphasized the loss of base as the all-important matter and specifically mentioned the danger as one accruing from a long-continued loss of base. His title "Zur Kenntnis der chronischen Ernährungsstörungen der Säuglinge" makes

3. Keller: Jahrb. f. Kinderh., 1897, xliv, 25.
4. Czerny and Keller: Jahrb. f. Kinderh., 1897, xlv, 274.
5. Howland and Cooke: Tr. Am. Ped. Soc., 1910, xii, 130.
6. Amberg and Morrill: Jahrb. f. Kinderh., 1909, lxix, 280.
7. Steinitz: Jahrb. f. Kinderh., 1903, lvii, 689. It may be pointed out here that Steinitz' contention presupposes that the alkali lost (chiefly sodium) is potential alkali and not merely a neutral salt. This has never been proven and is absolutely necessary for the substantiation of his hypothesis.

this sufficiently clear. Czerny[8] alone, apparently, has emphasized the immediate importance of the acidosis which was believed by him on the basis of Steinitz's work to be due to the loss of alkali. He thought that an explanation had thus been offered for the alteration of respiration, and that the relative acidosis might be severe enough to be the cause of death.

Ludwig Meyer[9] refused to commit himself on the importance of the acidosis (determined by an increased ammonia coefficient) on the development of "alimentäre Intoxikation." Tobler and Bessau[10] have discussed at length the ammonia coefficient and the microchemical staining methods for determining acid excess in the tissues and Salge's results (to be mentioned later). They conclude:[11] "There is still required an answer to the question whether any particular clinical picture or any complex of characteristic symptoms such, for instance, as those of *'alimentäre Intoxikation'* are found with one or the other of the various anomalies of metabolism that have here been described. According to the present standpoint of our knowledge the answer to this question must be 'No.' "

It would be going too far afield to discuss the significance of an increased ammonia coefficient. It is found in a great variety of conditions in which there is no other evidence of acidosis, and in such conditions as nephritis it is not a necessary accompaniment of acidosis. What should be emphasized is the fact that no sufficient evidence of the presence of acidosis has ever been brought forward, and that although acidosis has been spoken of in connection with nutritional disturbances, there has been no suggestion by anyone but Czerny that in the diarrheal diseases of infancy there may develop rapidly a severe and usually fatal acidosis not due to the production of acetone bodies. So far as we are aware, no one has made a practice of treating the acidosis with alkalies.

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8. Czerny and Keller: Die Ernährung des Kindes, Ernährungstörungen und Ernhrungstherapie, Vol. 2, p. 161.

9. Meyer: Jahrb. f. Kinderh., 1907, lxv, 608. "Es wäre verfrüht, heute, wo wir erst im Beginn der Forschung der Stoffwechselstörungen bei Intoxikationen stehen, etwa die markanteste Alteration des Stoffwechsels, die wir bei der Intoxikation beobachten konnten, die Acidose, als Ursache des Zustandes anzusprechen."

10. Tobler and Bessau: Allgemeine pathologische Physiologie der Ernährung und des Stoffwechsels im Kindesalter, Wiesbaden, 1914.

11. "Es bedarf noch die Frage der Beantwortung, ob irgend ein bestimmtes Krankheitsbild oder ein Komplex charakteristischer Symptome, wie etwa derjenige der sog. 'alimentären Intoxikation,' mit der einen oder anderen der hier besprochenen Stoffwechselanomelien zusammenfällt. Nach dem derzitigen Stand unserer Kenntnisse muss diese Frage verneint werden."

Salge[12] investigated, by means of the electrical method, the hydrogen ion concentration of the blood serum in ten normal infants and in a five weeks old infant with *Intoxikation*. He found the hydrogen ion concentration of the serum of the normal infants to vary between $10^{-7.2}$ and $10^{-7.63}$. That of the infant with *Intoxikation* was $10^{-4.84}$. In a subsequent communication[13] he reported one more case of *Intoxikation* in which the hydrogen ion concentration of the serum was $10^{-6.2}$. The accuracy of the determinations is seriously to be questioned, first, on account of the wide variations among the normal, and second, because of the virtual impossibility of ever finding such strongly acid serums during life. A concentration of $10^{-4.84}$ is one hundred times that of the maximum ever before reported, even in moribund animals poisoned with acids or in patients with diabetic coma, and a concentration of $10^{-6.2}$ is probably much greater than can ever occur in life.

CARBON DIOXID TENSION IN THE ALVEOLAR AIR

The disturbance of respiration (hyperpnea) occurring in many cases of severe diarrhea is such as to suggest that the respiratory center is strongly stimulated. This stimulation is due to an increase in the hydrogen ion concentration of the blood, *i. e.*, to a shifting of the reaction of the blood in the direction of acidity, though the blood always remains alkaline. Three years ago, therefore, we tested the blood of several infants suffering from diarrhea and hyperpnea, by the method devised by Sellards, and found a complete absence of color in the evaporated protein-free filtrate of the serum to which phenolphthalein had been added. Such a reaction as this is known to occur in cases of severe acidosis. On the basis of this information we have undertaken a systematic study of the whole question with the available methods. We have determined the tension or effective concentration of the carbon dioxid in the alveolar air. In acidosis there is a reduction of the carbon dioxid tension of the alveolar air which is roughly proportional to the severity of the acidosis. It was necessary, therefore, for us to establish figures for the carbon dioxid tension of the alveolar air of normal infants and to compare with these the results obtained in cases of infants suffering from diarrhea.

So far as we are aware, the carbon dioxid tension in the alveolar air of infants has not previously been determined, probably on account of the difficulty of collecting a sample, since in most methods devised for this purpose a certain amount of cooperation on the part of the

12. Salge: Ztschr. f. Kinderh., Orig., 1912, iv, 92.
13. Salge: Ztschr. f. Kinderh., Orig., 1913, vii, 292.

patient is necessary. The Plesch method, however, as modified by Higgins[14] has been successfully used on comatose adults, and we have adapted the procedure so that by the employment of a special mask it can be used for infants. The mask is made from the nipple of a wide-mouthed (Hygeia) nursing-bottle. A sheet of rubber tissue 8 by 10 inches is fastened to the lower rim of the nipple by means of rubber cement and adhesive plaster. The tip of the nipple is cut off and a short glass tube ⅜ inch in diameter is inserted in its place. In making a collection of alveolar air a rubber bag of 500 c.c. capacity is connected with the mask and partially filled with air by means of an aspirator bulb. The neck of the bag is closed off with a pinchcock or with the fingers, the mask is placed over the nose and mouth of the infant and the rubber tissue closely drawn around the face so as to prevent the escape of air. If possible, the mask should be placed over the face just at the end of expiration. Respirations are allowed to continue for from twenty-eight to thirty-two seconds, and at the end of an expiration the neck of the bag is closed off and the mask removed from the face. The air must be analyzed immediately, as diffusion occurs rapidly through the rubber and the composition of the air is altered. Analysis of the sample of air may be made with the Haldane apparatus[15] or more simply, and with a sufficient degree of accuracy, by the colorimetric method.[16]

We have found it necessary that the infant should have been breathing quietly for one minute previous to the collection of the sample of air, since vigorous crying just before the mask is put on leads to a lowering of the carbon dioxid tension by several millimeters. Crying during the collection of the sample, on the other hand, almost invariably occurs and facilitates the gaseous exchange. If the crying is very vigorous, the effect is to raise the tension somewhat, but not to such an extent as to be significant.

The initial amount of air in the bag must be such that during inspiration the bag is at least one-half, and preferably, as much as two-thirds, emptied, but not completely collapsed. The amount of air required for infants under 1 year of age varies from 250 c.c. to 400 c.c.

If the foregoing simple conditions are complied with, duplicate determinations usually agree within 2 mm. More than one determination should always be made, especially in confirmation of a low tension, as errors in technic usually lead to low figures. If the time of collection exceeds 32 seconds, too high a result is obtained.

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14. Boothby and Peabody: Arch. Int. Med., 1914, xiii, 497.
15. Haldane: Methods of Air Analysis, London, 1912.
16. Marriott: Jour. Am. Med. Assn., 1916.

In a series of normal infants the carbon dioxid tension in the alveolar air has been found to vary from 36 to 45 mm., as is shown in Table 1.

TABLE 1.—Carbon Dioxid Tension in the Alveolar Air of Normal Infants

Case	Tension, mm.	Case	Tension, mm.	Case	Tension, mm.
I	43.3	X	38.4	XVII	37.3
					39.8
II	42.3	XI	38.4	XVIII	39.2
III	44.5	XII	38.8	XIX	38.6
	43.2		42.2		38.2
			45.		
IV	43.		45.5	XX	39.
	43.				40.7
	45.7	XIII	38.6		
			40.	XXI	38.1
V	37.7		43.		
	37.4		40.	XXII	39.3
VI	38.2	XIV	39.6	XXIII	37.8
	36.2		41.8		
				XXIV	45.8
VII	39.6	XV	41.4		
			43.	XXV	43.2
VIII	37.				
	38.2	XVI	40.	XXVI	38.
	37.		38.4		
			38.8	XXVII	41.8
IX	37.4				

It will be seen that the figures fall within rather narrow limits. Several determinations on the same patient, often weeks apart, give nearly the same results. It is immaterial whether we determine the actual carbon dioxid tension of the alveolar air. What we wish to obtain is results that are nearly uniform in the normal child and that can be used for comparison with the sick.

A lowered tension of carbon dioxid is to be considered an indication of acidosis.[17]

In a considerable number of our cases of diarrhea, and in all cases of diarrhea in which an unmistakable hyperpnea was present,

17. For a discussion of the significance of carbon dioxid tension in the alveolar air, see Peabody: Am. Jour. Med. Sc., 1916, cli, 184. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, xxvii, 63. The method should not be applied to patients suffering from pulmonary complications. The administration of large quantities of caffein results in a lowering of the carbon dioxid tension; morphin exerts the opposite effect.

we have found a lowered tension of carbon dioxid in the alveolar air. The administration of an alkali to these patients has been followed by a cessation of the hyperpnea and a coincident return of the carbon dioxid to a normal or even abnormally high tension. Illustrative examples are given in Table 2.

TABLE 2.—CARBON DIOXID TENSION IN THE ALVEOLAR AIR OF INFANTS WITH ACIDOSIS

Case	Date	Carbon Dioxid, mm.	Hyperpnea	Alkali
I	9/22	21.2	+ + +	Given
	9/23	42.0	0	Given
	9/24	54.0	0	Stopped
	9/24	55.0	0	
	9/25	41.3	0	
II	9/28	18.0	+ + +	Given
	9/28	17.8	+ + +	Given
	9/29	21.3	+ +	Given
	9/30	32.8	+	Given
III	9/27	27.0	+ +	Given
	9/28	34.0	+	Given
	9/29	36.0	0	Given
IV	11/16	32.8	+	Given
	11/17	36.8	+	Given
	11/20	59.0	0	Stopped
	11/24	48.2	0	
	12/ 2	44.8	0	
V	....	27.8	+ +	
VI	....	30.4	+ +	
VII	....	24.4	+ + +	
VIII	....	27.0	+ +	
IX	4/16	28.8	+	Given
	4/17	33.	0	Given
X	....	25.2	+ +	
XI	....	21.	+ + +	
XII	....	14.3	+ + +	

HYDROGEN ION CONCENTRATION OF THE SERUM

Changes in the hydrogen ion concentration of the blood serum were determined by the dialysis indicator method devised by Levy, Rowntree and Marriott[18] with the modification later suggested by

18. Levy, Rowntree and Marriott: Arch. Int. Med., 1915, xvi, 389.

Marriott.[19] This gives the concentration of the serum as it is first obtained and after the carbon dioxid has been driven off by blowing. The latter figure is the more valuable index of acidosis as it allows of comparison under perfectly definite and constant conditions and is an indication of the effective alkali reserve. We have not found the hydrogen ion concentration of the serum of normal infants with its contained carbon dioxid to go beyond 7.4.[20] After removing the carbon dioxid, we have found it between 8.4 and 8.5. We have found that infants with diarrhea, hyperpnea and other evidence of acidosis often have a greatly increased hydrogen ion concentration of the serum. In severe cases, we have found it to be as great as 7.2 before

19. Marriott: Unpublished work.

20. The following description of physico-chemical notation is taken from the article by Levy, Rowntree and Marriott: Arch. Int. Med., 1915, xvi, 390.—"A solution is acid when it contains an excess of hydrogen over hydroxyl ions, neutral when hydrogen and hydroxyl ions are in equal numbers, and alkaline when hydroxyl ions predominate. An acid of 'normal' strength contains, in 1 liter, a gram of hydrogen capable of forming hydrogen ions, and its strength may be expressed as 1 N. Diluting such a solution ten times, we would have 1/10 N or a solution containing 1/10 gram of actual or potential hydrogen ions to the liter. Continuing the process of dilution until 1/10,000,000 normal acid is obtained, we would have in such a solution 1/10,000,000 gram of hydrogen ions. Pure water, however, dissociates to form hydrogen and hydroxyl ions, and at 200 C. contains approximately 1/10,000,000 gram of hydrogen ions to the liter and an equivalent amount of hydroxyl ions. That is to say, pure water, our standard of neutrality, is 1/10,000,000 N acid and also 1/10,000,000 N alkaline. To avoid writing large figures it is customary to use logarithmetic notation and to express 1/10,000,000 N as 10^{-7} N or, more conveniently, as suggested by Sörensen, to drop the 10 and minus sign and say pH7. If we have less than 1/10,000,000 gram of hydrogen ions to the liter, the solution is less acid than water, that is, it is alkaline—so, pH8 means actually 1/1,000,000 N alkaline. The higher the exponent the more alkaline, or what is saying the same thing, the less acid is the solution.

To sum up:

pH1 — N/10 acid
.
.
.
pH6 — N/1,000,000 acid
pH7 — Neutrality
pH8 — N/1,000,000 alkali
.
.
.
pH14 — N/10 alkali

(Ch7, pH7 and $(H^+) = 7$ are synonymous expressions. Intermediate values, as for example, between pH7 and pH8, are commonly expressed in one of two ways, as 0.25×10^{-7} or pH — 7.6. The latter method is used in this paper. The conversion of one expression into the other is simple. For example, log. $0.25 = -0.602$, then $0.25 \times 10^{-7} = 10^{-0.602} \times 10^{-7:0} = 10^{-7.602}$ or pH = 7.602.)"

removal of the carbon dioxid and to change only to 7.5 after removal of the carbon dioxid. A number of our results are shown in Table 3.

TABLE 3.—Hydrogen Ion Concentration of Serum in Acidosis

Case	With Carbon Dioxid	Without Carbon Dioxid
I	7.75	8.15
II	7.5	8.1
III	7.3	7.6
IV	7.2	....
V	7.2	7.55
VI	7.25	7.45
VII	7.3	7.9

SELLARDS' TEST

We have examined the sera of normal infants and of those in whom we had reason to suspect acidosis, by the method devised by Sellards.[21] This consists in evaporating the protein-free alcoholic extract of the blood serum to dryness with a few drops of phenolphthalein. Under normal circumstances, or, unless acidosis is present, a deep reddish purple color develops as evaporation proceeds, and the residue is purple and remains so. With many of our cases of severe diarrhea with hyperpnea the color was light pink or entirely lacking, though it sometimes developed on the addition of water. This alteration in behavior is to be taken as an evidence of acidosis of a marked degree of severity and probably indicates a serious diminution of the alkali reserve of the blood.[22] When sodium bicarbonate was given in sufficient quantity by mouth or intravenously, the color appeared after evaporation in the same manner as with normal patients.

In a number of our patients, the tolerance for alkalies (that amount which causes a distinct alteration in the reaction of the urine) has been determined. With normal infants 2 or 3 gm. of sodium bicarbonate are usually sufficient to bring about an alkaline reaction of the urine to litmus and to keep it alkaline for twelve or more hours. With acidosis, as was shown by Sellards[21] and later by Henderson and Palmer,[23] the amount of alkali must be greatly increased in order to bring about a similar change. An increased alkali tolerance is thus

21. Sellards: Bull. Johns Hopkins Hosp., 1914, xxv, 147.

22. Our observations were made before the introduction of the van Slyke apparatus for determining the alkali reserve of the blood. We have not used it with diarrheal cases up to the present time.

23. Henderson and Palmer: Arch. Int. Med., 1913 xii, 153.

to be looked on as an evidence of acidosis. With several of our patients, it was observed that four, five and even ten times the usual amount was necessary to alter the reaction of the urine.

HEMOGLOBIN DISSOCIATION CURVE

In confirmation of the other findings indicative of acidosis, we have studied the oxygen-combining power of the blood of our patients suffering from severe diarrhea.[24] Barcroft[25] has shown that the amount of oxygen combined with hemoglobin when it is saturated with oxygen at a given low tension is dependent on the hydrogen ion concentration of the mediums in which the hemoglobin is dissolved. With increasing acidity less oxygen is combined. If a normal blood is exposed to oxygen at a tension of 17 mm. in the absence of carbon dioxid, the hemoglobin is from 70 to 80 per cent. saturated. In our cases, with other evidences of acidosis, the hemoglobin under the same conditions has been only from 15 to 25 per cent. saturated. The hemoglobin dissociation curve is influenced by factors other than acidosis, for example, by salt concentration. Taken in connection with the other findings, however, the low dissociation curve may be considered as valuable confirmatory evidence of the presence of acidosis. Yllpö[26] determined the dissociation curve for the blood of infants suffering with nutritional disorders and found that the curve was normal except that just before death it was such as to indicate a severe acidosis. In our cases, however, we have frequently determined the presence of acidosis several days previous to death, and in some instances we have found unmistakable evidences of acidosis in patients who have subsequently recovered. The acidosis described in this present paper is not a terminal manifestation.

Theoretical objections might be raised against almost any of the methods available for the detection of acidosis. Realizing the possibility of experimental error to be greater than in most of the usual analytical proceedings, we have confirmed the presence of acidosis and have determined its degree by more than one method in all of our cases and have found a remarkable agreement in the results, both qualitatively and quantitatively. This is, in itself, proof of the acidosis and of the accuracy of the individual methods for its detection and quantitative determination.

It should be especially emphasized that acidosis does not occur in all cases of severe diarrhea. The majority of infants do not show evidences of it clinically or by the laboratory tests. It appears usually

24. We are indebted to Mr. H. L. Higgins for carrying out these determinations.

25. Barcroft: Respiratory Function of the Blood, Cambridge, 1914.

26. Yllpö: Deutsch. med. Wchnschr., 1915, xli, 782.

in illnourished children who have suffered somewhat recently from one or more attacks of digestive disturbance. Finally, a severe attack of diarrhea is precipitated and acidosis results. The clinical expression of the acidosis is hyperpnea. It is not always easy to determine by observation alone whether there is increased pulmonary ventilation. For this reason, slight hyperpnea may escape detection. Its severe forms can hardly do so. When hyperpnea with diarrhea has been undoubtedly present, we have not failed to find other evidences of acidosis, but on the other hand, we have determined the presence of acidosis when the increased pulmonary ventilation was not striking.

No other symptoms, so far as we have observed, are invariably associated with the acidosis in diarrhea. Very characteristic, however, are pallor and an ashen gray color of the skin in the absence of cyanosis, great restlessness gradually giving way to stupor and eventually coma, a markedly irregular temperature curve, a polymorphonuclear leukocytosis and, especially to be emphasized, a great reduction in the amount of urine often amounting to complete anuria. A characteristic history is the following:[27]

An infant was breast-fed for two months and did well, gaining weight satisfactorily and having no digestive symptoms. He was then weaned and given condensed milk. At the end of one month of this feeding he suddenly became irritable and began to vomit. Four days later diarrhea began and did not yield to treatment. He was moderately developed and nourished, but showed evidences of recent loss in weight. The skin was loose, hot and very dry. His eyes were deeply sunken and staring; his color gray but not cyanotic. His mouth was dry and his lips were parched. His fontanelle was depressed. His respirations were deep, heaving, pauseless, and were accomplished with distinct effort. His heart sounds were of poor quality. His liver was enlarged. He lay usually in a semi-stupor, but when roused, was very irritable and cried with a shrill, distressed cry. His white cells were 15,000. His temperature was between 99 and 101 F. His stools were large and consisted only of a brown, watery fluid. The carbon dioxid tension of his alveolar air was 15 mm. The bicarbonate of his blood was much reduced. The reaction of his blood had changed toward acidity and the combining power of the hemoglobin for oxygen was one fourth that of the normal. The acetone bodies in his blood were not increased. Despite the administration of alkali, by mouth and subcutaneously, he died eight hours after admission to the hospital.

The symptoms of the condition are essentially those given by Finkelstein[28] for *alimentäre Intoxikation*. This author has insisted on the necessity for the invariable presence of nine symptoms for the diagnosis of this condition. One of these is hyperpnea (*grosse Atmung*). He has not suggested any deduction to be drawn from the hyperpnea and apparently has not appreciated its significance, for

27. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, xxvii, 67.
28. Finkelstein: Jahrb. f. Kinderh., 1907, lxv, 1.

in a later article with Meyer,[29] he states that "The diagnosis of *Intoxikation* was made only if the symptoms which Finkelstein has demanded were present. Most important were the stupor, the fever and the loss of weight."[30]

CAUSE OF THE ACIDOSIS

Acidosis may result when abnormal acids are produced in excess in the body, when the kidneys fail to excrete acids normally produced, or, as Steinitz has assumed, when bases are lost from the body. We have examined the urine for the presence of acids of the acetone series, beta-oxybutyric acid and diacetic acid. As but small amounts of urine are passed, quantitative determinations of these substances have not been practicable, but qualitative tests have frequently shown no more than traces of acetone even in the presence of a severe acidosis. With acidosis due to the acetone bodies, examinations of the blood give more valuable information than examinations of the urine, as it is the acids that are retained that harm the organism and not those excreted in the urine. We have consequently determined the beta-oxybutyric and diacetic acid in the blood by the micro-method devised by one of us.[31]

We have found acetone bodies in excess of the normal amounts in the blood of these patients, but never in amounts comparable to those that are found in acidosis due to the accumulation of these substances in cases of recurrent vomiting and other conditions.[32] Normally, the total acetone bodies in infants vary from 5 mg. to 15 mg. per one hundred c.c. of blood.

Associated with simple starvation in an infant 20 months old, we have seen the acetone bodies rise to 40 mg. at the end of forty-eight hours, but with no symptoms of acidosis and no appreciable alteration in the reaction of the blood. In the cases of diarrhea that have shown well-marked acidosis, the acetone bodies have varied in amount from 15 to 30 mg. per one hundred c.c. of blood, an amount entirely insufficient to account for the acidosis. In cases of ileocolitis, larger amounts of the acetone bodies may be found in the blood with a normal reaction of the blood and an alveolar air within normal limits.* There is no reason to suppose that acetone bodies play any significant part in the production of the acidosis occurring in the course of

29. Finkelstein and Meyer: Jahrb. f. Kinderh., 1910, lxxi, 720.

30. "Die Diagnose der Intoxikation wurde erst gestellt, wenn die Symptome. die Finkelstein gefordert hat, vorhanden waren. Vor allem die Benommenheit, das Fieber und Gewichtsabfall."

31. Marriott: Jour. Biol. Chem., 1914, xviii, 507.

32. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, xxvii, 63.

*A discussion of the acetone bodies in the blood in ileocolitis and other conditions is reserved for a later communication.

the diarrheal conditions of the type that we have described in this paper. The acetone bodies produced may be considered to be the result of partial starvation and to have no especial relation to the underlying conditions.

It is possible that lactic acid may enter in as a factor in the production of the acidosis, but at present we have not sufficient evidence to prove or disprove this assumption. We are at present engaged in the investigation of this phase of the problem. As has been mentioned previously, Keller[33] was unable to find abnormal organic acids in the urine of infants suffering from diarrheal diseases.

Conceivably, acidosis may result from loss of base from the body, by way of the intestinal tract. Steinitz[7] found a negative sodium and potassium balance in infants fed on high-fat diets, especially if there was a concomitant diarrhea with loss of weight, and has considered this as evidence of an alkali loss from the body. His results do not prove the point, for he failed to determine the acid constituents also lost from the body. That there should be a negative balance of all food constituents in a diarrhea with loss of weight is not to be wondered at. A negative sodium balance would occur if sodium chlorid were eliminated in excess in the stools; the relation between acid and base in the body, however, would not be altered at all. Holt, Courtney and Fales[34] have confirmed the results of Steinitz as to loss of sodium and potassium in diarrhea. They found however that, while sodium and potassium excretion by the bowel was greatly increased, the excretion of chlorid was increased still more! The alkali is lost from the body but acid is also lost. From the work published up to the present time no conclusions can be drawn as to whether acid or alkali predominates in the loss.

By a method devised in our laboratory, and as yet unpublished, it has been determined that in some cases with diarrheal stools there is a loss of potential acid rather than potential alkali, whereas normally there is usually a slight alkali loss. These results will be the subject of a subsequent communication.

One possibility remains as an explanation for the acidosis, namely, a failure of the acid excretory function of the kidney. Under normal conditions the kidney excretes a very considerable amount of acid, chiefly in the form of acid phosphate. A failure of this special function of the kidney would result in a retention of acid phosphate and a consequent acidosis. In severe diarrhea, the urinary secretion may be markedly diminished even to the point of complete anuria, the kidney becoming functionally more or less inactive, even though no

33. Statement by Steinitz: Monatschr. f. Kinderh., 1902, i, 225.
34. Holt, Courtney and Fales: Am. Jour. Dis. Child., 1915, ix, 213.

organic changes may be present. That diminished acid excretion and consequent retention of acid phosphate in the body fluids would occur under these conditions would seem probable. We have a certain amount of experimental evidence in support of this hypothesis; that is to say, we have found an increase in the phosphate content of the blood serum in the course of severe diarrhea, but are not as yet prepared to say that this is surely and solely the cause of the acidosis. Further experimental work is required before this can be definitely established from the quantitative standpoint. Retention of acid phosphate, without doubt, could cause acidosis, and in the light of our present knowledge, we consider this, perhaps, the most probable explanation of the acidosis occurring with severe diarrhea.

TREATMENT

It is necessary to consider here only the treatment of the acidosis that complicates the diarrhea. To the accepted methods of treating the diarrhea itself we have at the present time nothing to add. So long as the ultimate cause of the acidosis remains obscure, we cannot employ direct measures to prevent its development. The acidosis may result, though it has not yet been proved, from loss of bases by the intestinal tract. The excessive diarrhea should be prevented, if possible, by moderate doses of opium, for, in any event, the draining of the body of water cannot be an indifferent matter. Opium in some form, such as paregoric, may be given, preferably in small doses, frequently repeated, to be reduced or stopped when the evacuations diminish in frequency or copiousness. Water must be given freely by mouth, if possible; if vomiting prevents this, as it frequently does, it must be given by rectum, subcutaneously or intravenously.

If, as has been suggested above, the acidosis is due to the retention of acid phosphates, the excretion of these substances and the consequent prevention of acidosis would be greatly facilitated by a copious secretion of urine. When acidosis develops, the secretion of urine is very scanty and often ceases for hours at a time. Under such circumstances it is most difficult to increase the activity of the kidneys. All measures should be used to prevent the cessation of the activity. The best of these is the constant administration of water or salt solution in one of the ways mentioned above.

When the presence of the acidosis is determined by the hyperpnea or by some laboratory test, energetic treatment is required. Alkalies must be administered promptly, until the reaction of the blood is again normal. We have used sodium bicarbonate for this purpose. This may be given by mouth, by rectum, subcutaneously or intravenously. Vomiting often prevents the administration by mouth, and absorption

by the bowel is unreliable in the presence of diarrhea. The soda may then be given subcutaneously or intravenously. When a sufficiently large vein can be found, intravenous administration is the method of choice, even if there is no vomiting. Immediate action can thus be obtained. The strength of the solution for intravenous use is 4 per cent. Depending on the size of the infant, from 75 to 150 c.c. should be given and repeated in three hours if the hyperpnea does not cease. A large amount of alkali is required, for not only is the alkalinity of the blood reduced but also that of all the tissues of the body. After one or two intravenous injections, the soda should be continued by mouth in doses of 1 to 3 gm. every two or three hours until the urine is alkaline to litmus. Should it be impossible to give the soda intravenously, the solution may be injected subcutaneously. There is always danger under such circumstances that necrosis of the tissues will result. The danger is minimized, if certain precautions are taken. The solution (either 2 or 4 per cent.) is sterilized by heat. By this procedure, however, a large part of the bicarbonate is transformed into the carbonate. As the carbonate is intensely irritating to the tissues, it must be transformed back into the bicarbonate. This may be done by bubbling carbon dioxid through the cold solution to which a few drops of phenolphthalein have been added until it becomes colorless.[35] From 100 to 300 c.c. may be employed at an injection and should be given very slowly.

The administration of soda by one or the other method will often overcome both the clinical and laboratory evidences of acidosis. We have frequently seen the hyperpnea disappear and all the tests show the reactions to be found in the normal infant. Nevertheless, the child may die—indeed, such is usually the case. The cause of death under such circumstances is not clear. It is possible that as the result of the acidosis certain processes have been initiated which render life impossible or certain others may have been inhibited without which life is impossible. It is sufficiently clear that the condition resulting from or accompanying the acidosis is most serious even if its exact nature is not understood. Therefore in all cases of severe diarrhea, even though there are no evidences of acidosis, it is advisable to use sodium bicarbonate until the urine is alkaline. Its administration may prevent the development of acidosis. When further observations have made clear the processes on which the acidosis depends, we may be able to direct our treatment more intelligently. At the present time we are forced to combat the result and not the cause.

35. Magnus-Levy: Therap. Monatsh., 1913, xxvii, 838.

The following cases are cited to show that severe or even fatal diarrhea may occur without any evidence of acidosis:

CASE 1.—G. Z., 5½ months old. Strong, vigorous child at birth. Breast-fed for one month; thereafter, condensed milk, and later, modified milk. Gained weight very slowly and was poorly nourished but without definite symptoms except furunculosis. Diarrhea began suddenly on the day before admission to the hospital. Numerous large stools (twenty-four) in past twenty-four hours. No hyperpnea. Color gray. Carbon dioxid tension in alveolar air, 35 mm. Sellards' test gave deep purple color; pH, 7.75 and 8.35 after removal of carbon dioxid. Sodium bicarbonate, 3 gm. by mouth, caused an alteration in the reaction of the urine. Trace of acetone bodies in urine. Acetone bodies in blood, 30 mg. per one hundred c.c. The child died forty-eight hours after admission.

CASE 2.—A. S., 7 months old. Full-term child. Breast-fed for two months and did well. Then weaned and given milk, tea, coffee and bread. Illness began twelve days before entering hospital. Frequent loose, green stools. Temperature, 101 to 104 F. No hyperpnea. Carbon dioxid tension of alveolar air, 45.8 mm.; pH, 7.85 and 8.4 after removal of carbon dioxid. Acetone bodies in blood, 23 mg. per one hundred c.c. Died twenty-four hours after admission.

The following cases are fair examples of fatal diarrhea with acidosis:

CASE 3.—E. M., 3 months old. Vigorous child at birth. Weight, 8¾ pounds. Nursed for two months and thereafter given condensed milk in the day and nursed at night. Ill from the time of weaning. For four days before admission had vomited and refused food. Stools, frequent, large and watery. Marked hyperpnea. Carbon dioxid tension of the alveolar air, 14.3 mm.; pH, 7.2 and 7.55 after removing carbon dioxid. Hemoglobin dissociation, 17.8 per cent. at 17 mm. Acetone bodies in blood, 19 mg. per one hundred c.c. Died four hours after admission.

CASE 4.—R. S., 6 months old. Weight, 8¼ pounds at birth. Nursed for two months; thereafter given milk and water, equal parts, whenever hungry, as well as crackers and scraps from the table. Four days before admission, vomiting and diarrhea began. Stools every few minutes, yellow and watery. Temperature, 101 F., rising to 107.5 F., just before death. Marked hyperpnea. Carbon dioxid tension of alveolar air, 25 mm.; pH, 7.3 and 7.9 after removing carbon dioxid. Sellards' test, positive (no color). Acetone bodies, 21 mg. per one hundred c.c. Died twenty hours after admission. Necropsy findings negative except for slight congestion of mucous membrane of colon.

CASE 5.—T. B., 6 months old. A small child at birth. Nursed for two months, then weaned and given a mixture of milk, water and sugar. Weight at 6 months, 12 pounds. Onset, acute, twenty-four hours before admission to the hospital. There was vomiting after every feeding and a profuse, watery diarrhea. Ten stools in twenty-four hours. Child much prostrated. Hyperpnea marked. Carbon dioxid tension of alveolar air, 21 mm.; pH, 7.25 and 7.45 after removing carbon dioxid. Hemoglobin dissociation, 13 per cent. saturation at 17 mm. Acetone bodies in blood, 22 mg. per one hundred c.c. Death occurred eight hours after admission. Necropsy showed slight ulceration in the ileum and colon, hyperplastic mesenteric lymph nodes and a fatty liver.

CASE 6.—A. A., 7 months old. Nursed for two months; thereafter given condensed milk. For two weeks had had frequent loose green stools, containing mucus. Admitted to the hospital in a wretched condition. Weight, 9.5 pounds. Hyperpnea not present. Carbon dioxid tension of alveolar air, 30 mm.; pH, 7.75 and 8.15 after removing carbon dioxid. Sellards' test nega-

tive. Sodium bicarbonate, 4.5 gm., given by mouth, causing a rise of the carbon dioxid tension of the alveolar air to 35 mm. After 12 gm. of soda, the urine became alkaline.

The child did well for four days, but at the end of this time, developed a pneumonia which was quickly fatal. The acidosis in this case was mild and was readily overcome. It was not sufficient to cause so marked an increase of pulmonary ventilation as to be recognized as hyperpnea, nor was the reduction of the alkali of the blood sufficient to cause a positive Sellards' test. The low carbon dioxid of the alveolar air and the increased hydrogen ion concentration of the blood serum showed unmistakably that acidosis was present.

SUMMARY

Acidosis is found in many cases of severe diarrhea not of the ileocolitis type. The clinical expression of the acidosis is hyperpnea.

The presence of the acidosis has been confirmed by determining a lowering of the carbon dioxid tension of the alveolar air, by an increase in the hydrogen ion concentration of the blood serum, by a diminution of the alkali reserve of the serum, by an increase in the amount of alkali required to alter the reaction of the urine (alkali tolerance) and by a diminution of the combining power of the hemoglobin with oxygen.

It has been shown that the administration of sodium bicarbonate will often bring about a cessation of the hyperpnea and cause the laboratory tests to give the results that are found with normal infants.

The acidosis is not due to the presence of acetone bodies. It has not been demonstrated that it is due to loss of base. It is probable that it is due to deficient excretion of acid phosphate by the kidneys.

Johns Hopkins Hospital.

STUDIES IN THE METABOLISM OF CHILDREN

I. THE EXCRETION OF CREATININ AND OF CREATIN IN ACUTE NEPHRITIS *

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OMAHA.

It is to be expected that the excretion of creatin and of creatinin during acute nephritis in the child will show variations from the normal and from the adult normal; for it has been known for several years, through the earlier work of Amberg and Morrill[1] and the later investigations of Rose, of Folin, and of Sedgwick, that creatin, an unusual component in the adult, is a normal constituent of children's urine and that the relation between relative muscle mass and creatinin output, which holds for the human organism at and beyond puberty[5] breaks down in children at earlier ages. Again, many investigations demonstrate nitrogen retention in cases of nephritis, experimental and pathologic.[6] As far as we are aware, however, it has not been determined what occurs in the child under such conditions. There are a few isolated reports[7] bearing on the point but they are not of a character to assist us in a rationale of child metabolism with respect to the components with which this paper is concerned. Very valuable determinations of the creatin and creatinin content of the blood of nephritic subjects have been made on adults,[8] indicating the character of retention.

In the present paper, we present the data derived from a study of two children[9] aged 5 and 13, whose cases were followed for periods of

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* Submitted for publication Feb. 17, 1916.

* From the Biochemical Laboratory of the University of Nebraska College of Medicine, Omaha.

1. Amberg and Morrill: Jour. Biol. Chem., 1907, iii, 311.
2. Rose, W. C.: Jour. Biol. Chem., 1911, x, 265.
3. Folin, O.: Jour. Biol. Chem., 1912, xi, 253.
4. Sedgwick, J. P. R.: Tr. of the Section of Diseases of Children, A.M.A., 1910, p. 105.
5. Folin, O.: Am. Jour. Physiol., 1905, xiii, 66. Van Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1905, xlvi, 415.
6. Mosenthal, H. O.: Arch. Int. Med., 1904, xiv, 844; Proc. Soc. Exp. Biol. and Med., 1915, xiii, 9. Folin and Denis: Jour. Biol. Chem., 1914, xvii, 487. Davis and Foster: Proc. Soc. Exper. Biol. and Med., 1915, xiii, 33. Older literature in Roseman, R.: Arch. f. d. ges. Physiol., 1898, lxxii, 467.
7. E. g., Mohr, L.: Ztschr. f. klin. Med., 1903-4, li, 331.
8. Folin and Denis: Jour. Biol. Chem. 1914, xvii, 487.
9. We express our obligations to Dr. B. W. Christie, physician to the Clarkson Hospital, Omaha, for the opportunity to study these cases.

thirty-five days and ten days, respectively. The former, a boy, H. J., was under the care of a special nurse, the latter, likewise a boy, R. Mc., was attended by the floor nurses. In both cases, especial care was given to the collection of the daily twenty-four hour specimens of urine. The diets in each case were practically creatin and creatinin-free, being administered for minimum protein maintenance, calculated in calories.[10] In the case of R. Mc., the temperature (Fig. 1) was practically normal except at the beginning of the disease. Inasmuch as pyrexial conditions of whatever origin have been shown to modify the tolerance for creatinin and for creatin,[11] it is important to have these data in hand. In the other case, H. J., the temperature chart was not available.

The urines were deproteinized by the use of colloidal iron. The creatinin determinations were made according to the usual Folin method, the creatin by difference according to the modification by S. R. Benedict[12] of Folin's original method.

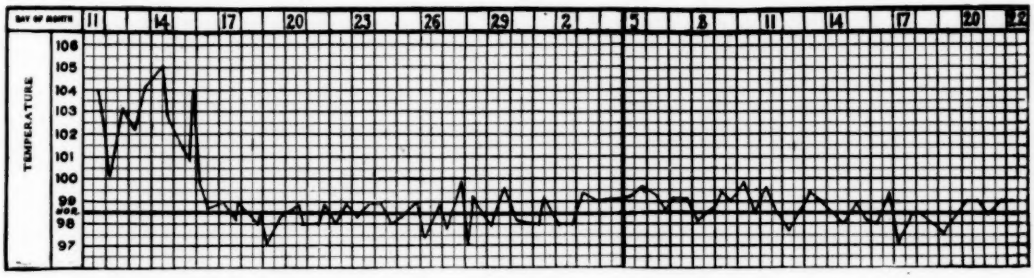

Fig. 1.—Temperature Chart for Case of R. Mc.

The most conspicuous feature of the curves of excretion of both constituents and in both cases is the wide variation from day to day. Moreover, this variation, which approaches a rhythm, is independent of all known concomitant factors, such as food, temperature, etc. It appears that a threshold exists which, on being reached, leads to excretion of the creatin and creatinin. Retention in the sense of almost if not quite total suppression of excretion of these components does not exist for a period of more than twenty-four hours. In fact, there is a *negative* balance in every instance in which a period of one week

10. A typical diet for both cases is that of November 18: Breakfast, 6:30 a. m., cereal (cooked) 2 tablespoonfuls, cream, ¼ pint; 9:30, milk, 8 oz. Lunch, 12 m., bread, 1 slice, butter (50 cal.), potato (1 baked). Dinner, 5:30 p. m., cereal (as at 6:30 a. m.), bread (as at noon), butter (as at noon), cream (as at 6:30).

11. Leathes, J. B.: Jour. Physiol., 1906-7, xxxv, 205. Shaffer, P. A.: Am. Jour. Physiol., 1908, xxiii, 1, p. 13.

12. Benedict, S. R.: Jour. Biol. Chem., 1914, xviii, 191.

or over is considered. We have here then, apparently, a condition which varies markedly from that which has been reported for the adult, in whom retention of creatin and creatinin is described.[13]

The curves exhibit no correlation between the behavior of creatinin and that of creatin. It is impossible to determine anything which might suggest an origin of one from the other.

For comparison with normal children, a study of creatin and creatinin excretion in several boys and girls of ages varying from 9 months to 12 years was made.[14] The results obtained are given in Table 1.

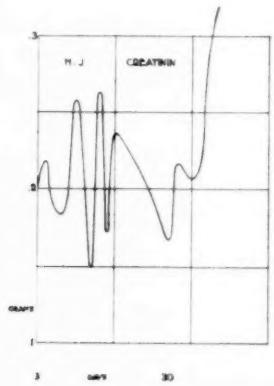

Fig. 2.—Curve 2: creatinin elimination in "H. J."

TABLE 1.—CREATIN AND CREATININ EXCRETION IN CHILDREN

Case	Age (yrs.)	Creatin in 24 hours.	Creatinin in 24 hours.
A	5	0.00*	0.312
B	3	0.040	0.130
C	3	0.00*	0.348
D	3	0.010	0.251
E	3	0.135	0.130
F	4	0.00*	0.310
G	¾	0.274	0.245
H	3	0.089	0.323
I	11	0.570	0.870
J	1	0.070	0.059
K	12	0.510	0.760
L	8	0.110	0.550

* Not determined.

Judging from these figures, the averages for the two cases of nephritis are somewhat low. This is not to be interpreted without

13. Lampert, D.: Ztschr. f. klin. Med., 1914, lxxx, 498, where a review of the subject may be had.

14. The writers cannot express too warmly their appreciation for the painstaking care with which these samples were furnished us by Miss Réné MacKenzie, R.N., of the Child Saving Institution, Omaha.

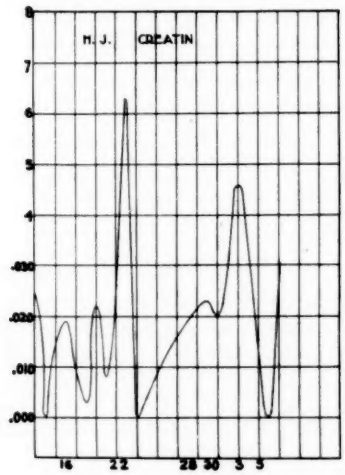

Fig. 3.—Curve 3: creatin elimination in "H. J."

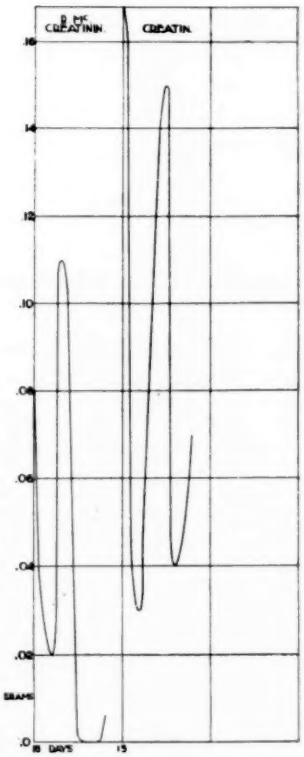

Fig. 4.—Creatinin (to 15), creatin (part 15), for "R. Mc."

analysis as retention, for in the cases of nephritis we are dealing with the child at rest. Moreover, this immobility is in itself a condition which approaches the abnormal, or pathologic. While we are aware that exercise does not apparently affect the output of creatinin or of creatin in the adult, yet in children inactivity in itself is conducive to a loss of tone and sometimes of weight. Hence we must not assume, until more figures are obtained from further study, that the lower output of these children means retention in the sense in which biochemists speak of nitrogen retention.

It is desirable to mention one difficulty in the study of creatin and creatinin metabolism in very young children and in children in whom there is a retention of these components even during a twenty-four hour period, namely that of reading the colorimeter when small amounts of creatinin are present. Our results were obtained by the dilution method, that is, by diluting the urine according to the amount of creatinin present. Amberg and Morrill and others have concentrated the urines, but this seems to us to be precarious. Therefore, though the figures that we give must have an element of error in them, the error is constant and inasmuch as we desire relative data, the results are adequate. Inasmuch as there was, throughout, no sugar present, no attention was given to the possible modification of the creatin fraction. From the observations of Wolf and Osterberg[16] and others, unless acetonuria and glucosuria are pronounced, the creatin fraction is not materially modified.

CONCLUSIONS

1. Retention of creatinin and of creatin nitrogen in the cases of nephritis in children presented here is a matter of less than twenty-four hours.

2. The excretion of these components varies widely from day to day and their amounts are not correlative with pyrexial, nor with other known conditions.

3. No other quantitative study similar to the present one has been made as far as we are aware.

4. There is a wide divergence between the data reported for adults and those determined by us for children.

Forty-Second and Dewey Avenues.

16. Wolf, C. G. L. and Osterberg, L.: Am. Jour. Physiol., 1911, xxviii, 71, Cathcart and Orr: Jour. Physiol., 1914, xlviii, p. xxi.

STUDIES IN THE METABOLISM OF CHILDREN

II. CREATIN RETENTION IN MARASMUS *

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OMAHA

The fact seems established, through the investigations of many workers,[1] that in the adult, fasting involves an increase in the excretion of creatin. As far as we are aware, this condition has not been identified in the young. Fasting, however, affects the creatin output differently in different species of animals, for while in the adult of the human species, an increase in this component is observed, the reverse is the case in starving dogs.[2] McCollum and Steenbock[3] find the pig refractory under the influence of starvation.

Mellanby[4] reported a case of cyclic vomiting (recurrent vomiting) in a boy of 6 in which marked loss in weight occurred during the attacks. He speaks of creatin excretion in a child of 6 as being an abnormality and says also that there was an increase in creatin excretion two and three days *before* the attack, during which and after which loss in weight occurred. It is not possible to draw satisfactory conclusions from this paper.

In a similar investigation, Sedgwick[5] reports abnormal creatin excretion (an augmentation) during attacks of recurrent vomiting in several cases of children from 2 to 10 years of age. The data exhibit no correlations with loss in weight, but the rise in creatin runs *pari passu* with the appearance of febrile conditions.

In the case which we present herewith, there is a clear *lowering of creatin excretion during a long period of loss in body weight.* The weight curve is given in the chart. Vomiting occurred after each intake of food *per os,* due, apparently, to pyloric spasm[6] and this condition did not cease entirely after the growth curve began to rise, following the use of mother's milk (Oct. 16, 1915). Creatin deter-

* Submitted for publication Feb. 17, 1916.

* From the Biochemical Laboratory of the University of Nebraska College of Medicine, Omaha.

1. Van Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1905, xlvi, 415.
2. Howe, Mattill and Hawk: Jour. Biol. Chem., 1912, xi, 103.
3. McCollum and Steenbock: Jour. Biol. Chem., 1912, xiii, 209.
4. Mellanby, E.: Lancet, London, 1911, ii, 8.
5. Sedgwick, J. P.: AM. JOUR. DIS. CHILD., 1912, iii, 209.
6. This diagnosis was made by the attending physician, Dr. Clyde Moore, whose interest in the case and whose kindness made it possible to study it carefully. To Miss Réné MacKenzie of the Child Saving Institute we are especially indebted.

minations were made by the Folin method and by Benedict's modification, practically identical results being given in the two cases, The creatinin excretion apparently was normal for a child of that age (2) and rose gradually, as in the normal child, regardless of the growth curve. All data refer to twenty-four hour amounts, the samples being taken by a modifcation of the method of Schabad.[7]

CREATININ AND CREATIN EXCRETION IN A CASE OF MARASMUS

Date	Creatinin Gm.	Creatin Gm.
10/ 2/15	0.144	0
10/13/15	0.144	0
10/15/15	0.195	0
10/19/15	0.201	0
10/25/15	0.212	0.028
10/29/15	0.218	0.050
11/ 8/15	0.295	0.072

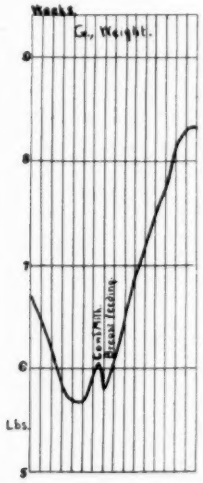

Chart of weight curve in case of marasmus.

CONCLUSION

In the case of a male child of 2 years, whose curve of growth gradually fell on account of pyloric spasms, the creatin excretion remained practically suppressed until the growth curve began to rise consequent on breast feeding. Creatinin excretion remained normal during the whole period.

Forty-Second and Dewey Avenues.

7. Schabad, J. A.: Arch. f. Kinderheilk., 1908, xlviii, 402.

TWO CASES OF OBSTETRICAL PARALYSIS INVOLVING ONLY THE MUSCULOSPIRAL NERVE*

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WASHINGTON, D.C.

With the exception of facial nerve palsies, paralysis of a single peripheral nerve present at the time of birth is a rare condition. Clear descriptions of musculospiral paralysis of the newly born cannot be found in the literature. The two cases here reported came under observation in the outpatient department of the Harriet Lane Home of the Johns Hopkins Hospital.

REPORT OF CASES

CASE 1.—Oct. 3, 1914, B. B., a girl, 19 days old, was brought to the dispensary by her mother because she did not move her left hand.

Family History.—Father 28 years old; mother 25 years old; both healthy; two children in addition to the patient, 3 years old and 9 months old, respectively; both normal; no history of miscarriage or stillbirths, or of lues.

Past History.—The patient was born spontaneously, at term, after a precipitate labor. The mother had been having pains throughout the day of September 14, and in the evening called in the midwife who had attended her at the birth of the two other children. The midwife found the mother up and about, getting supper. Three hours later the midwife was hurriedly summoned and before there was any time to assist, the baby "popped out into the bed," as the midwife described it. One loose coil of cord about the neck was easily removed. Slight cyanosis was present. The baby is said to have weighed 8 pounds.

Following birth, the baby had no convulsions or sickness of any kind, nursed well and was not cyanosed; no evidence of congenital lues. Nothing abnormal about her was noted except the local condition in the left arm presently to be described.

Eight days after birth the mother first noticed that the baby did not move the left hand as she did the right. The left hand looked to her deformed, but did not seem to be in any way painful.

Physical Examination.—A well-nourished baby, 19 days old, weighing 8 pounds, 10 ounces; temperature normal; head, well formed; anterior fontanel normal in size and tension; pupils equal and react to light; extra-ocular movements normal; no ptosis; eardrums normal; no facial paralysis; superficial lymph nodes not enlarged; thorax normally shaped; heart normal; lungs clear; contour of abdomen normal; liver edge felt just below costal margin; spleen not felt; genitalia normal; the legs and the right arm are moved by the child freely, in all directions, in an entirely normal manner.

The left upper arm is kept in very much the same position as the right upper arm, but the left forearm is held flexed at the elbow, so that it forms a right angle with the upper arm, and the hand is held in the typical position of wrist-drop. The upper arm can be moved in all directions by the child, exactly like

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* From the Harriet Lane Home and Department of Pediatrics, Johns Hopkins University.

the right, but although the child can flex the forearm when it is passively extended, there is never any attempt at extension of the forearm against gravity; in fact, when the forearm is extended passively, there is an immediate return to the position of flexion. The fingers can be extended slightly when they are flexed, but there is no limitation of flexion. The wrist-drop remains constantly present, unless the hand is passively brought into a position of extension or falls into a position of extension from gravity, but as soon as the forearm is held upright, and the support of the hand in the position of extension released, the hand tumbles back into the position of wrist-drop. There is no hindrance to passive motion either in the muscles or joints, nor does passive motion seem to be painful. No bony deformity can be felt anywhere. The contour of the humerus, as felt through the soft parts, is entirely normal. On examination of the different muscles, so far as it is possible to do this accurately in so young a child, it is found that the deltoid, biceps and flexors of the wrist and fingers act normally, while the triceps, supinators and extensors of the wrist, and to a less degree, the extensors of the fingers, have no power at all. The paralysis is, then, limited to the distribution of the musculospiral nerve.

The Roentgen-ray examination shows a normal condition. The Wassermann is negative.

Oct. 15, 1914: (Baby 31 days old). Electrical examination by Dr. Taneyhill shows reaction of degeneration (galvanic stimulation) in triceps, extensor muscles of the wrist and supinator longus; reaction of deltoid normal.

Oct. 22, 1914: The condition of the left arm remains the same; electrical reactions, which are repeated, unchanged.

Nov. 5, 1914: Some movement in the triceps is noted; reaction of degeneration plainly visible in anconeus; still present in extensors of wrist and supinator longus.

Dec. 10, 1914: Noticeable improvement; only feeble reaction of degeneration in triceps and extensors of wrist.

Feb. 18, 1915: The left arm is entirely normal. The pathologic condition has disappeared without leaving a trace of its existence.

CASE 2.—May 13, 1915, O.T., a girl, 13 days old, was brought to the Harriet Lane Dispensary by her mother from the obstetrical department of the Johns Hopkins Hospital, for routine examination previous to discharge.

Family History.—Father, 24 years old; mother, 19 years old; both healthy; no other children, but the mother had a miscarriage at the second month, nine months previous to the birth of the patient; no history of lues.

Birth History.—The baby was born spontaneously, at term, after long, difficult labor; mother's pelvis funnel shaped. Presentation, L.O.A.; first stage 59 hours, 14 minutes; second stage 1 hour 24 minutes; third stage 8 minutes, making a total of 60 hours, 46 minutes; mother was given narcophin 0.5 gm. and scopolamin 0.045 gm.; one injection of narcophin and scopolamin and four injections of scopolamin alone were given. The first dose was administered 6 hours and 46 minutes before delivery, with the cervix 6 cm. in diameter; pains every four minutes. Chloroform was given at end of labor, 10 c.c. for 20 minutes; 1 c.c. of pituitary fluid was given during second stage; mother very restless and restrained with difficulty; child apneic; hot and cold tubs given for 30 minutes; artificial respiration necessary; heart action good from the first.

Past History.—Immediately after birth it was noted in the obstetrical department that marked asymmetry of the face and chest existed. The right side of the face and thorax were flattened and pushed inward as if considerable pressure had been present during labor. This asymmetry disappeared by the second day. It was also noted, immediately after birth, that the left hand was held flexed on the forearm and that the hand was in the typical wrist-drop position, and also that on the outer surface of the left upper arm, a short distance above the external condyle, a small, reddish tumor-like swelling was present. The birth weight was

5 pounds, 15 ounces. The baby had no fever or convulsions and did not develop any symptoms suggestive in any respect of lues. She nursed normally every three hours. The stools were normal.

Physical Examination.—May 13, 1915: Thirteen day old baby, weighing 5 pounds, 5 ounces; head normally shaped; anterior fontanel normal in size and of normal tension; pupils, equal and react to light; no strabismus or ptosis; ear drums normal; no facial paralysis; no enlargement of superficial lymph nodes; thorax, well formed, without showing any evidence of the asymmetry which was noted immediately after birth; heart normal; lungs clear; liver edge felt at level of umbilicus, in right mammillary line; spleen not felt; both legs and the right arm are moved by the child freely in all directions and show no abnormality.

The left arm is held semiflexed at the elbow and the hand is flexed on the forearm in a position of wrist-drop. On stimulating active motion, it is found that the child can move the arm in a normal manner at both the shoulder and elbow joints, and extend the forearm against gravity. The child, too, can slightly supinate the hand but cannot be made to extend the fingers, which are held in a flexed position. After the fingers and wrist are extended passively, they immediately drop back into their former position. No sign of pain can be elicited by palpation and no bony deformity can be found in any of the bones of the forearm, or about the shoulder girdle on the left side. The deltoid, triceps, biceps and flexors of the wrist and fingers have normal power. The supinators and extensors of the wrist and fingers seem, however, to be paralyzed. The paralysis in this case also appears limited to the distribution of the musculospiral nerve .

On the outer surface of the upper arm about 2 cm. above the external condyle is an oval, red, elevated area, situated with its long axis in the long dimension of the arm. It is about 3 cm. long and 1.5 cm. wide. It seems to lie chiefly in the deep tissues and to involve the skin, but to be freely movable on the bone below, though it is not absolutely certain that it may not be connected with the bone by a pedicle. The center of the tumor is softer than the periphery and fluctuates, while the rather broad border surrounding the fluctuating area is indurated and firm. Palpation of the area does not seem to be painful, though it is not positively certain that no pain is present. Aspiration of the mass results in withdrawal of a few drops of a thick, yellowish-white material, which, when stained and examined with the microscope shows only a cellular detritus with some disintegrating, swollen cells, thought probably to have been pus cells, but no organisms of any kind. On the following day the mass was again aspirated and a few drops of bloody fluid were obtained, apparently chiefly composed of fresh blood. No organisms were seen in the smears from this fluid, and cultures planted on agar mediums were sterile.

May 20, 1915: The mass is distinctly smaller, measuring now 2 by 1 cm.; no fluctuation can be obtained, but the central part of the mass feels distinctly depressed, as if a loss of substance had taken place in its central part. The character and extent of the paralysis are exactly the same as at the first examination. Electrical examination by Dr. Taneyhill shows reaction of degeneration of the supinator longus and extensors of the wrist; biceps, triceps and deltoid, normal.

June 12, 1915: (Baby 43 days old). The skin is only very slightly indurated over the site of the mass on the outer side of the arm and there is no evidence of any paralysis whatsoever. The child moves the left hand and fingers exactly as the right.

DISCUSSION

The commonest form of obstetric paralysis is the well-known upper arm or Duchenne-Erb type, first accurately described by Duchenne,[1] but often called Erb's paralysis; incorrectly, however, since Erb's description was of a similar condition in the adult produced by injury to the fifth and sixth cervical roots.[2]

Next in frequency is the rather rare form of obstetric paralysis known as the lower arm or Klumpke[3] type, which is concerned with the disturbance of the lower roots of the brachial plexus, the seventh and eighth cervical and first dorsal roots, and gives rise to symptoms chiefly in the distribution of the ulnar and median nerves. Since the ramus communicans between the eighth cervical and the first dorsal and sympathetic is also injured, certain eye signs, such as narrow lid slit and contracted pupil on the same side as the lesion, may be present and aid in the localization of the injury.

The third form of birth palsy is in reality merely a combination of the two forms just described, and may be of such severity as to give rise to a complete paralysis of the arm.

The pathogenesis of these forms of obstetric paralysis is not absolutely certain. It seems most likely that the upper arm type is produced by stretching of the roots of the brachial plexus, while there may be actual rupture of the nerve trunks in severe cases. Theoretically any manipulation which tends to widen the angle formed by the neck and shoulder in delivery should tend at the same time to stretch the roots of the brachial plexus on that side, if severe enough, with injury even to the point of rupture. It is not so easy to explain the pathogenesis of the lower arm type of obstetric paralysis, but the series of cases collected from the literature by J. J. Thomas[4] indicates that the majority are connected with breech delivery.

Other causes have been advanced to explain injury to the brachial plexus in obstetric paralysis, such as fracture or separation of the upper epiphysis of the humerus, dislocation of the shoulder or fracture of the clavicle. But when present, these pathologic conditions of the bones or joints attest rather to the severity of the strain to which the parts were subjected than to a specific injury to the plexus by the fracture or dislocated bone itself.

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1. Duchenne: Paralysies obstétricales infantiles du membre superieur, sans complications. De 'électrisation, Ed. 3, 1872, p. 537.

2. Erb: Handbuch der Elecktrotherapie, Ed. 2, 1886, p. 305.

3. Klumpke: Paralysies radiculaires du plexus brachial, Rev. d. méd., 1885, v, 591.

4. Thomas, J. J.: Two cases of Bilateral Birth Paralysis of the Lower Arm Type, Boston Med. and Surg. Jour., 1905, cliii, 431.

Injury to a single peripheral nerve may occur (1) before, (2) during or (3) after labor. The single nerve most commonly injured is the facial, and the injury is due usually to direct pressure of the forceps on the nerve itself.

Prenatal cases of paralysis of the musculospiral nerve, due to the pressure of amniotic bands about the arm, have been reported by Bonnaire,[5] Spieler,[6] Cassirer[7] and Ballantyne[8] and reference to this condition is made by Cautley[9] in his textbook, and also by Zappert[10] in his discussion of obstetric paralysis in Pflaundler and Schlossman's work. In each of the cases reported, pressure marks of the constricting band were visible on the arm, showing the site of the lesion and also its causation.

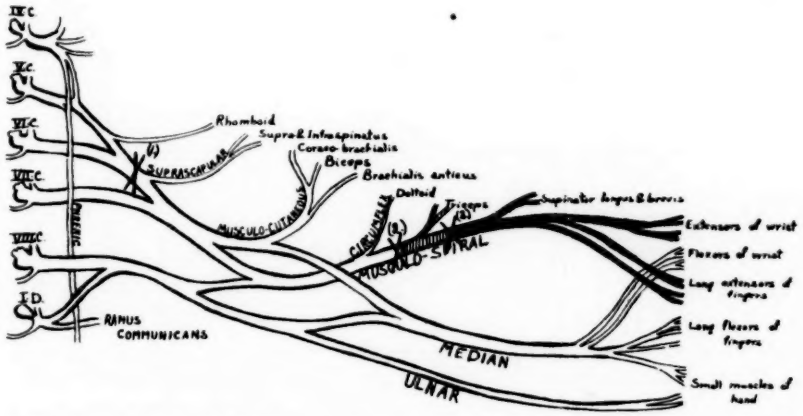

Diagram of Brachial Plexus.—1. Region of "Erb's Point." 2. Case 1: The site of the lesion in the musculospiral nerve is between its branch to the deltoid (circumflex) and its branches to the triceps. 3. Case 2: The site of the lesion is distal to the muscular branches to the triceps but proximal to the branches given off to the supinator muscles.

Injury to the musculospiral nerve at the time of birth may be secondary to bone injury, particularly of injury to the humerus, as is readily understood when the close anatomic relationship that exists between the musculospiral nerve and the humerus is considered. T. T.

5. Bonnaire: (Case) Centralbl. f. Gynäk., 1898, xxii, 914.

6. Spieler: Einen Fall von traumatischen Radialislähmung, Jahrb. f. Psychiat., 1903, xxiii, 415.

7. Cassirer: Ueber Schadigung Nerven durch intrauterin entsandene Schnurfurchen, Deutsch. med. Wchnschr., 1905, xxxi, 1221.

8. Ballantyne: Antenatal Pathology and Hygiene, p. 186.

9. Cautley: Diseases of Infants and Children, 1910.

10. Zappert: Organic Diseases of the Nervous System, Pflaundler and Schlossmann, 1908, iv, 262.

Thomas[11] reports a case of musculospiral paralysis shown by the presence of wrist-drop associated with dislocation of the head of the humerus, with improvement after the dislocation was released. Kramer[12] and Gangolphe[13] have reported musculospiral paralysis in connection with the fracture of the humerus, and Bernhardt[14] gives a fracture of the bones of the lower arm as a possible cause.

Injury to the peripheral nerves after birth is exceedingly rare in infants and young children. "Children do not appear to be very liable to injury of the nerves in spite of the many accidents which befall them. I have not seen a case of traumatic neuritis in the plexus of a child below the age of 14 years excepting the form of brachial neuritis just described" [obstetrical paralysis].—(Starr.)[15] Gowers[16] mentions the fact that musculospiral paralysis is not uncommonly found in Russian infants as a result of a popular practice of binding the arms to the body and then laying the child on its side. Bernhardt,[14] Hirt[17] and Gibson-Fleming[18] also give this as a cause.

Burr[19] reports a number of obstetric paralyses in which he assigns the lesion to the motor cells of the cord, conceiving of the condition as an unusual manifestation of poliomyelitis.

Instances of musculospiral paralysis due to birth injury appear in the literature, but no accurate descriptions of them have been given. Ott[20] says relative to this condition, "When the nerve is injured high up, the triceps muscle is paralyzed. Then you may have as in one case of mine *where the nerve was injured during the birth of the child*, loss of power to extend the forearm and of supination of the hand." Haslinger[21] reports a case in which a paresis of the left facial nerve was noted immediately after birth and five days later peripheral paralysis in the distribution of the right musculospiral nerve. The tri-

11. Thomas, T. T.: Laceration of the Axillary Portion of the Capsule of the Shoulder Joint as a Factor in the Etiology of Traumatic Combined Paralysis of the Upper Extremity, Ann. Surg., 1911, liii, 77.

12. Kramer: Nervenverletzungen, Lewandowsky's Handbuch der Neurologie, ii.

13. Gangolphe: Paralysie radiculaire traumatique du plexus brachial, Lyon méd., 1906, cvii, 977.

14. Bernhardt: Die Erkrankungen der peripherischer Nerven, Nothnagel's Handbuch, 1895, xi.

15. Starr: Nervous Diseases, Organic and Functional, 1913, p. 179.

16. Gowers: Diseases of the Nervous System, Ed. 2, 1892, i, 85.

17. Hirt: Musculo Spiral Paralysis, Diseases of the Nervous System, 1899.

18. Gibson-Fleming: Diseases of Spinal Nerves, Allbutt and Rolleston's System of Medicine, 1911, vii.

19. Burr: Spinal Birth Palsies; A Study of Nine Cases of Obstetrical Paralysis, Boston Med. and Surg. Jour., 1892, cxxvii, 235.

20. Ott: Clinical Aspect of Some Peripheral Palsies, Philadelphia Med. Times, 1884, xv, 268.

21. Haslinger: (Reference), Centralbl. f. Gynäk., 1899, xxiii, 1173.

ceps in Haslinger's case remained normal. Fairbank[22] states that a wrist-drop may be a residual paralysis of a more extensive birth palsy, the bulk of which has been entirely recovered from. Zappert[10] makes mention of a case in which musculospiral paralysis was the result of intrapartum pressure on the nerve, but does not describe it in further detail. Oppenheim[23] makes the statement, "It is not common for obstetric paralysis to be limited to this nerve (musculospiral) or to affect it chiefly, though I have observed this."

The distribution of the paralyses in these two cases is limited to the muscles supplied by the musculospiral nerve. *No muscle not supplied by the musculospiral nerve was affected.* In Case 1 the supinators and extensors of the wrist and the triceps were paralyzed; in Case 2 only the supinators and extensors of the wrist.

The fibers of the sixth, seventh and eighth cervical roots pass not only into the musculospiral nerve, but also into the nerves supplying the deltoid, biceps and flexors of the wrist, so that these latter muscles are affected in addition to those supplied by the musculospiral nerve when the injury lies in the sixth, seventh and eighth cervical roots. Since the deltoid, biceps and flexors of the wrist were unaffected in the two cases under discussion, the lesion cannot lie in the cervical roots, but must lie peripheral to them, in the musculospiral nerve itself. The site of the lesion in the musculospiral nerve must lie, in Case 1, between its branch to the deltoid (the circumflex), which was not paralyzed, and its branches to the triceps, which were paralyzed. The lesion in Case 2 must lie lower down, distal to the muscular branches to the triceps, but proximal to the branches given off to the supinator muscles, since the triceps remained intact while the supinators were affected.

If the causes of peripheral palsies affecting the upper extremities of infants are considered, it is possible to exclude the majority of them without difficulty as being operative in these two cases. It is possible to exclude antenatal injury in its only well-recognized form, namely, pressure from amniotic bands, as a causative factor. The surface of the arm was entirely normal in Case 1, and the mass described on the outer side of the arm in Case 2 might, perhaps, when first seen, have been considered of inflammatory nature or as a new growth, but not, by any possibility, as the pressure mark of a constricting band. It is possible, also, to exclude in both cases traumatism from a dislocated or fractured bone, as neither of these conditions was present. Nor is it possible to think that the musculospiral nerve was injured after birth in these two patients, for their arms were not

22. Fairbank: A Lecture on Birth Palsy; Subluxation of the Shoulder Joint in Infants and Young Children, Lancet, London, 1913, i, 1217.

23. Oppenheim: Lehrbuch d. Nervenkranken, Ed. 2, 1898, p. 320.

bound to the body, nor did either infant receive any injury or trauma. It is scarcely necessary to consider poliomyelitis as a possible cause when it is remembered that the paralysis in one case was noted immediately after birth, and that in the other case the baby had had no fever or shown any sign of acute illness. Moreover, the limitation of the paralysis to a peripheral distribution in both cases is most difficult to explain on the basis of motor cell injury in the anterior horn. The paralysis cannot be regarded as the residual of a birth paralysis which was originally more extensive. The muscles, other than those described as being paralyzed, were entirely normal in both cases a few days after birth, as was determined by careful examination. The paralyses in obstetric palsies do not disappear as rapidly as this. Restitution to the normal, if it occurs at all, is a matter of weeks or months rather than of days. Moreover, if the paralysis had been originally more extensive, the lesion must have been higher up in the plexus in the fifth and sixth cervical roots. If this had been the case, why should the fibers in the roots passing to the musculospiral nerve be the only ones severely affected, while those passing into the circumflex and musculocutaneous remained essentially unaffected?

It is impossible to determine exactly what was the manner of production of the paralysis in Case 1, but it seems almost certain that the injury must have occurred during the birth of the child. It is a very common experience, particularly in dispensary practice, to find that extensive obstetric paralysis is not noticed for a considerable period after birth, and when it is suddenly brought to the attention of those about the child, the inference is made that it has been recently acquired. It is practically certain in Case 2 that the injury to the musculospiral nerve was acquired during birth. It is established that the mother had a funnel-shaped pelvis and that the labor was long and difficult; in other words, that the conditions for pressure injury in the child were present, and that the child immediately after birth showed evidences, in the asymmetry of the face and chest on the opposite side to the lesion in the arm, that she had been subjected to extreme degrees of pressure.

It is exceedingly interesting that the mass which was described as situated on the outer surface of the arm about 2 cm. above the external condyle should exactly overlie the musculospiral nerve at the calculated point of injury. It is impossible to say exactly what this mass was. Apparently it was not inflammatory, because the smear from it showed no organism and it was sterile on subsequent culture. Moreover, it spontaneously disappeared, so that it cannot be explained on the basis of tumor. It seems probable, particularly from its subsequent behavior, that the mass was a hematoma, although it is difficult to understand how the child acquired a hematoma in

this particular place. There is no evidence that the arm could have been caught in any way against the pelvis, as might have been the case, for example, if the arm had presented extending downward between the pelvis and the head. In any event, it seems highly probable that the mass and the paralysis in Case 2 were associated, since the mass exactly overlay the point at which the nerve must have been injured. Both were probably the result of a common pressure exerted during passage of the child through the pelvis. Complete healing took place in both cases in an exceedingly short time, a fact which indicates that the injury to the nerve was relatively mild, and in the nature of a contusion rather than a laceration.

The following additional references may be consulted:

Clark, Taylor and Prout: A Study on Brachial Birth Palsy, Am. Jour. Med. Sc., 1905, cxxx, 670.

Thomas, H. M.: Obstetrical Paralysis, Infantile and Maternal, Bull. Johns Hopkins Hosp., 1900, p. 279.

THE PERMEABILITY OF THE GASTRO-ENTERIC TRACT OF INFANTS TO UNDIGESTED PROTEIN*

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I. INTRODUCTION

The possible absorption of unaltered or incompletely digested protein is a question of more than academic interest. It is well established that the introduction of foreign protein into the circulation may provoke certain specific reactions (formation of precipitins, sensitization, etc.). Nutritional disturbances in infants fed on cow's milk have been attributed to the biologic character of the food. According to our present conceptions the specific biologic properties of animal tissues reside in great part, if not entirely, in the protein constituents. It is generally believed, however, that the proteins are split into amino-acids before absorption. If such is universally true, biologic reactions to cow's milk would be unlikely, as it has been demonstrated that specificity is lost in protein cleavage products lower than the peptones.

Ganghofer and Langer[1] found that the intestinal tract of young animals permitted the passage of heterologous protein (beef, egg) as determined by precipitin tests applied to the blood serum. When physiologic quantities were given, this occurred only in animals less than eight days old. After this time the tests were not positive, except with massive doses of the foreign protein or when the intestinal tract was subjected to chemical injury. In two debilitated infants, absorption of undigested egg protein was demonstrated by precipitin tests applied to the blood.

Mayerhofer and Pribam[2] observed that in acute enteritis there was an increased permeability of the intestinal wall to both crystalloids and colloids. Hamburger and Sperk[3] could not demonstrate absorption of foreign protein when small quantities were fed, nor did they find

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* From the Laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons, and the New York Nursery and Child's Hospital, New York.

1. Ganghofer and Langer: Ueber die Resorption genuiner Eiweisskörper im Magendarmkanal neugeborener Tiere und Säuglinge, München. med. Wchnschr., 1904, li, 1497.

2. Mayerhofer, E., and Pribam, E.: Ueber die Beeinflussung der Diffusionsvorgänge an frischen tierischen Darmmembranen, Biochem, Ztschr., 1910, xxiv, 453; Das Verhalten der Darmwand als osmotische Membran dei akuter und chronischer Enteritis, Wien. klin. Wchnschr., 1909, xxii, 875.

3. Hamburger, F., and Sperk, B.: Biologische Untersuchungen über Eiweissresorption vom Darm aus, Wien. klin. Wchnschr., 1904, xvii, 641.

an increased permeability of the intestinal tract to undigested protein in young animals. Uffenheimer's[4] experiments led to the same conclusion.

On the other hand, Lawatschek* has recently found that the intestinal tract of very young infants is more permeable to foreign protein.

Uhlenhuth[5] found that prolonged feeding of egg protein to rabbits caused the development of specific precipitins in the blood, thus indicating the entrance of egg protein into the general circulation. In healthy men Ascoli[6] was able to demonstrate the presence of egg protein in the blood serum by precipitin tests as early as one and three-fourths hours after the egg was ingested. In the urine, egg protein and human protein could be demonstrated. Inouye[7] obtained practically the same results.

Moro[8] found milk precipitins in the blood of two out of twenty-two investigations on atrophic infants (postmortem). In one case there was complement deviation for milk protein. Bauer[9] demonstrated precipitins and also complement deviation for milk in the blood of four atrophic infants.

In contrast to these positive results Krasnogorski[10] did not find precipitable milk protein in the urine of infants suffering from nutritional disorders.

Recent experiments by Modigliani and Benini,† however, indicate that casein may be absorbed unaltered. Their technic consisted of

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* Lawatschek: Die enterale Resorbtion von genuinen Eiweiss bei Neugeborenen und darmkranken Säuglingen, etc. Prag. Med. Wchnschr, 1914, xxxix, 185.

† Permeability of Intestinal Tract of Infants for Casein of Cow's Milk, Policlinico, Dec. 1915, abstr. in Jour. Am. Med. Assn, 1915, lxiv, 475.

4. Uffenheimer, A.: Zur Frage der intestinalen Eiweiss Resorption, Jahrb. f. Kinderh., 1906, lxiv, 383.

5. Uhlenhuth: Neuer Beitrag zum spezifischen Nachweis von Eiereiweiss auf biologischen Wege, Deutsch. med. Wchnschr., 1900, xxvi, 734. Haendel: Untersuchungen über die praktische Verwertbarkeit der anaphylaxie zur Erkennung und Unterscheidung verschiedener Eiweissarten, Ztschr. f. Immunitätsforsch., 1910, iv, 761.

6. Ascoli, M.: Ueber den Mechanismus der Albuminurie durch Eiereiweiss, München. med. Wchnschr., 1902, xlix, 398; Neue Tatsachen und neue Ausblick in der Lehre der Ernährung, München. med. Wchnschr., 1903, i, 201.

7. Inouye: Ueber alimentare Albuminurie, Deutsch. Arch. f. klin. med., 1903, lxxv, 378.

8. Moro, E.: Kuhmilchpräzipitin im Blute eines 4½ Monate alten, Atrophikers, München. med. Wchnschr., 1906, liii, 214.

9. Bauer, J.: Ueber den Nachweis der precipitablen Substanz der Kuhmilch im Blute atrophischer Säuglinge, Berl. klin. Wchnschr., 1906, xliii, 711.

10. Krasnogorski, N.: Ueber die Herkunft des Harneiweiss bei Albuminurien der Säuglinge, Ztschr. f. Kinderh., 1912, iv, 526.

testing the blood serum of infants affected with gastroenteric disorders with anti casein serum from rabbits. The patients were receiving cow's milk as food.

The results obtained by means of anaphylactic tests on animals are closely analogous to those in which the precipitin test was used. Rosenau and Anderson[11] and others showed that the feeding of foreign protein caused the animal to become sensitized to the protein fed. This indicated that some of the protein, at least, was absorbed in a partially digested state. Vaughan, Cummings and McGlumphy[12] demonstrated, by anaphylactic tests, that rabbits absorb incompletely digested protein through the gastro-enteric tract. After feeding egg protein the blood of rabbits was capable of sensitizing guinea-pigs to egg protein. Van Alstyne and Grant,[13] and Van Alstyne,[14] found that dogs absorb foreign protein through Thiery-Villa fistulas in sufficient quantities to sensitize guinea-pigs. In a patient subject to alimentary albuminuria they found that the protein in the urine sensitized both to the foreign protein fed and to human protein. This observation is in accord with the work of Uhlenhuth and others with the precipitin test.

Lust[15] has recently studied the absorption of heterologous protein by infants affected with nutritional disorders. The precipitin test applied to the urine was the means of identification, though in some cases the anaphylactic test was used. His results showed that in normal infants undigested egg or beef protein is not absorbed. In nutritional disorders he found that egg protein appeared in the urine after ingestion. Beef protein was absorbed unchanged in very few cases. The experiments of Hyashi[16] and Lawatschek gave results similar to those of Lust.

Our own investigations were undertaken in the effort to determine the possibility of absorption of undigested protein by infants. For this purpose precipitin and anaphylactic tests were used and the blood was examined for the presence of reaction substances (protective ferments of Abderhalden).

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11. Rosenau and Anderson: Studies on Anaphylaxis, Bull. Hygienic Lab., 1908, No. 45.

12. Vaughan, Cummings and McGlumphy: The Parenteral Introduction of Proteins, Ztschr. f. Immunitätsforsch., 1911, ix, 16.

13. Van Alstyne, E., and Grant, J. P.: The Absorption of Albumin Without Digestion, Jour. Med. Research, 1911, xxv, 399.

14. Van Alstyne, E.: Absorption of Protein Without Digestion, Arch. Int. Med., 1913, xii, 372.

15. Lust: Die Durchlässigkeit des Magendarmkanales für heterologes Eiweiss bei ernahrungsgestarten Sauglingen, Jahrb. f. Kinderh., 1913, lxxvii, 244 and 283.

16. Hayashi, J.: Ueber die Durchlässigkeit des Sauglingsdarmes für artfremdes Eiweiss und Doppelzucker, Monatschr. f. Kinderh., 1914, xii, 749.

II. ABSORPTION OF UNDIGESTED PROTEIN BASED ON THE EXAMINATION OF THE URINE BY PRECIPITIN AND ANAPHYLACTIC TESTS

In many of the experiments cited the tests for foreign protein were applied to the blood. On first thought this may seem the ideal method, but as applied to infants it has at least one insurmountable obstacle. It has been shown by Ascoli, Lust and others that the foreign protein is present in the blood stream for a very short time and the detection of its presence would require frequent examinations, obviously a procedure not permissible in infants, especially those affected with nutritional disorders. On the other hand, it has been found that the foreign protein is present in the urine over a longer period of time. The following observation made by one of us (S.) has a direct bearing on this question.

C. J. S., aged 21 years, subject to alimentary albuminuria.

The patient was given the whites of ten eggs at 8 a. m. on an empty stomach. The urine was collected every hour and blood removed at intervals of one or two hours. Two cubic centimeters of urine or citrated blood were injected into the peritoneal cavity of guinea-pigs as a sensitizing dose to test for egg protein by the anaphylactic reaction. Two weeks later the animals were given 2.5 c.c. of egg white as an intoxicating dose. Two animals, weighing from 250 to 300 gm., were used in each experiment. The results are given in Table 1.

TABLE 1.—THE PRESENCE OF EGG PROTEIN IN THE BLOOD AND URINE AFTER INGESTION OF EGG WHITE. ANAPHYLACTIC TEST

Hour	Albuminuria Heat and Acetic Acid	Anaphylactic Test Blood	Anaphylactic Test Urine
7:45 a. m.	—	—	—
8:00 a. m. egg ingested	—		—
9:00 a. m.	—	±*	—
10:00 a. m.	—	++	—
11:00 a. m.	Faint trace	—	+
12:00 m.	Heavy trace	—	++
1:00 p. m.	Marked	..	+++
2:00 p. m.	Trace	—	++
3:00 p. m.	—	..	—*

* ± equals questionable reaction; + equals mild, ++ marked and +++ severe reaction.

This observation demonstrates that the foreign protein appears in the blood stream earlier, but persists in the urine for a longer time. In consideration of these results and the factors already discussed, the tests in our observations were applied to the urine.

1. *Precipitin Tests.*—The precipitating serum for egg white was obtained from rabbits in the usual way by giving three or more intravenous injections of 2.5 c.c. of egg white. The second and third injections were given at intervals of four and three days, respectively. If, after the third injection, the egg serum exhibited a titer of 1:100,000 or more, the animal was bled to death, the serum passed through a Berkefeld filter and preserved in sealed glass capsules until used. Otherwise, further injections of egg white were given until a serum of sufficient strength was obtained. No serum with a titer of less than 1:100,000 was used, and in some instances it ranged from 1:500,000 to 1:1,000,000.

In accordance with the experience of others, it was found impossible to obtain regularly a milk precipitating serum of high titer. Many animals were treated with milk, whey, casein, and the whey proteins precipitated by saturation with ammonium sulphate. One animal treated by the last method gave a serum with a titer of 1:20,000. This serum was used for tests to be described later. Further trials by the same procedure were futile, though the technic was as nearly as possible identical to that first used. Serums were obtained with titers of 1:300 to 1:700, but, owing to the negative results of Krasnogorski with such serums, they were considered inadequate.

The precipitin tests for milk were carried out on mixed specimens of urine from infants fed on cow's milk. In the egg tests the infants were fed the whites of from one to two eggs and the urine collected for six hours used for the examination. In all cases the urine was tested pure, diluted 1:5, 1:10, 1:50 and 1:100 with normal saline. Two-tenths cubic centimeter of the precipitating serum was added to each tube containing 1 c.c. of the plain or undiluted urine. The tubes were incubated at 37.5 C. for one hour and the results noted. They were placed on ice for twelve hours, and in case a definite precipitate was not apparent in the tubes considered positive after one hour incubation, the test was regarded as negative. Cases in which the precipitate appeared only after twelve hours were also considered negative. In each experiment, control tests were carried out with 0.2 c.c. of normal rabbit serum in place of the precipitating serum, and also with 0.2 c.c. of the precipitating serum added to normal urine. The urines were all faintly acid or amphoteric to litmus, and, when at all concentrated, were dialyzed through collodion for twenty-four hours before the test was applied.

DISCUSSION

The results relating to cow's milk are shown in Tables 2, 3 and 4. Judging from these results, in normal infants fed on cow's milk no foreign protein recognizable by the precipitin test appears in the urine. Two of the four atrophic infants tested excreted protein in the urine which gave a positive test with milk precipitating serum. The results in gastro-enteric disorders[17] were identical. In two of the four cases

17. We make no attempt to follow any definite clinical or pathologic classification of these cases. The term gastro-enteric disorder is merely used to designate nutritional disturbances characterized by loss of weight, vomiting, loss of appetite, frequent bowel movements of more fluid consistency than normal, of abnormal color and odor. The terms mild, moderate and severe refer mainly to the general disturbances such as loss of weight or appetite, fever, vomiting and symptoms of intoxication. In the absence of a satisfactory etiologic classification we feel that it is safer and perhaps clearer to classify the cases in this way rather than to attempt classification based on pathologic lesions, the supposed infecting micro-organism or an apparent intolerance to an individual food substance.

observed a precipitate was obtained in the urine when treated with the anti-whey serum.

These results indicate, therefore, that in atrophy or gastro-enteric disorders whey protein may be absorbed from the gastro-enteric tract without complete digestion and appear in the urine. Krasnogorski, using the precipitin and complement deviation tests obtained negative results in similar observations. His precipitating serum, however, had a titer of 1 : 600 while ours was 1 : 20,000. This probably explains the difference in results. As mentioned previously, Modigliani and Benini were able to show that casein may be absorbed by infants affected

TABLE 2.—PRECIPITIN TESTS FOR COW'S MILK IN URINE OF NORMAL INFANTS

Number	Age, Months	Weight, Pounds	Albuminuria, Heat and Acetic Acid	Precipitin Reaction
1	5	14½	—	—
2	5	13¾	—	—
3	6	15	—	—
4	6	15½	—	—
5	8	17	—	—
6	8	19	—	—

TABLE 3.—PRECIPITIN TESTS FOR COW'S MILK IN URINE OF INFANTS SUFFERING FROM ATROPHY

Number	Age, Months	Weight, Pounds	Albuminuria, Heat and Acetic Acid	Precipitin Reaction
1	5	9	—	Negative
2	7	8½	Faint trace	Positive pure, 1-5
3	8	8	—	—
4	9	9½	Trace	Positive pure, 1-5

TABLE 4.—PRECIPITIN TESTS FOR COW'S MILK IN URINE OF INFANTS SUFFERING FROM ACUTE GASTRO-ENTERIC DISORDERS

Number	Age, Months	Weight, Pounds	Albuminuria, Heat and Acetic Acid	Precipitin Reaction
1	3	9	Trace	Positive pure
2	6	11¾	—	—
3	8	13½	—	—
4	8	13	Faint trace	Positive pure, 1-5, 1-10

with intestinal disease. The precipitin tests with egg protein are shown in Tables 5 to 10 inclusive. Tests were made on fourteen infants without symptoms of gastro-enteric disturbance. In one infant egg protein appeared in the urine after the ingestion of the whites of two eggs, although the test was negative when one egg white was ingested. In another case the test was positive when the whites of one and one-half eggs were given. In the remaining twelve normal infants there was no evidence of absorption of unaltered egg white.

These results indicate that, when given in moderate amounts, egg white is absorbed by normal infants only after complete digestion; or, to be strictly accurate, none of the foreign protein appears in the urine. Our observations differ from those of Lust in that two positive results were obtained in experiments on fourteen normal infants. His results were entirely negative.

Seven infants with mild gastro-enteric disorders were tested. (Table 6). In two cases egg protein was excreted in the urine. In one of these the test was negative after the ingestion of one egg but was positive when two eggs were given.

In three of the four cases of moderate severity tested (Table 7), positive results were obtained. Case 4 is of special interest since it was possible to make four tests at different stages of the disease. At the onset of the disease the test was negative. During the period of maximum severity the test was positive and after improvement was negative.

Of the six cases with severe symptoms all showed a positive reaction at some time during the disease (Table 8).

Six cases of eczema were investigated and the result was positive in three.

Considered collectively these results show that after the ingestion of moderate amounts of egg white normal infants rarely excrete egg protein in the urine recognizable by the precipitin test. In gastro-enteric disorders the mucous membrane becomes permeable, the degree of permeability being in direct ratio, apparently, to the severity of the disorder. These results practically coincide with those of Lust.[18] Judging from the results in six cases there is a tendency for infants with eczema to absorb incompletely digested egg white.

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18. In the interpretation of our results, we assume that the appearance of precipitable egg protein in the urine is indicative of its absorption in undigested or incompletely digested forms. While this assumption is in accord with accepted ideas, there are other possibilities which must be mentioned: (1) That small amounts of undigested egg protein may be absorbed but destroyed or fixed in some organ so that it does not appear in the urine; (2) that the absorption of small amounts of partially digested egg protein is usual, and the appearance of the foreign protein in the urine is not a direct indication of its absorption, but rather of the failure of the normal mechanism for its destruction.

2. *Anaphylactic Tests.*—When the urine contained coagulable protein (heat and acetic acid, cold nitric acid, tests) it was precipitated by saturation with ammonium sulphate and the precipitant removed by dialysis through collodion. A quantity of this protein solution equivalent to 3 c.c. of the urine was injected into the peritoneal cavity of a 250 to 300 gm. guinea-pig. This served as the sensitizing dose. In the absence of albuminuria 3 c.c. of the urine was used for this purpose. After the lapse of twenty-one days an intoxicating dose of 2 c.c. of egg white was given intraperitoneally. The animals were watched closely and the symptoms recorded. All equivocal reactions were excluded. The symptoms on which the degree of shock was estimated were as follows:

Mild: Uneasiness accompanied by bucking movements. Roughening of coat. Sneezing, scratching of nose, neck and forelegs. Slight to moderate dyspnea accompanied by indrawing of sides. Slight fall of temperature—1.6 to 2.5 F.

Moderate: The above symptoms in greater degree, with especial reference to fall of temperature, dyspnea and weakness.

Severe: Paralysis of hind limbs. Convulsions. Fall of temperature from 5 to 8 F. Often death. Marked distention of lungs at necropsy.

DISCUSSION

Analysis of the results shown in Tables 5 to 10 admits of the following summary:

After the ingestion of egg by normal infants, the urine did not sensitize to egg white though in two cases a positive precipitin reaction occurred.

The test was negative in two cases of mild gastro-enteric disorder, though in one of these the precipitin reaction was positive.

Of the cases of moderate severity the anaphylactic test was positive in one of three cases tested. In all three the precipitin reaction was obtained.

Eight of the severe cases were tested and in five the test was positive. In all of the urines positive with the anaphylactic test the precipitin reaction was also positive.

The urine of two of the three patients with eczema tested sensitized guinea-pigs to egg protein. In both the precipitin reaction was present.

Ten cases of malnutritition or atrophy were observed and in five the test was positive. It was never positive in the presence of a negative precipitin reaction, though in three cases with a positive precipitin test the anaphylactic reaction was absent.

The general conclusions to be drawn from the results of the two tests are identical, though the precipitin reaction was positive in a greater number of cases than the sensitization test. The precipitin reaction was often present in urines apparently free from coagulable protein (clinical tests). The anaphylactic test, however, seemed to bear a direct relationship to the presence of clinical albuminuria following the ingestion of egg. It was never possible to sensitize guinea-pigs to egg white with urine which gave no precipitate with heat and acetic

acid. In a few instances protein-containing urine did not sensitize to egg white, but in the greater number of such cases the albuminuria was entirely independent of the ingestion of egg.

Of considerable interest is the fact that human urine, free from coagulable protein, can sensitize to human protein. This fact has been pointed out by Wells,[19] Uhlenhuth and others. It would thus seem that human protein derivatives below the coagulable forms are capable of sensitizing to the whole protein.

Our results offer a possible explanation for the rather contradictory results of Ascoli and others who used the precipitin test, and of Wells[19] who used the anaphylactic reaction, as the means of identification of egg protein in human urine. As mentioned previously, Ascoli and others detected biologically precipitable egg protein in the blood and urine of normal individuals after the ingestion of egg. Wells, on the other hand, could not sensitize guinea-pigs to egg protein with the urine of patients who had ingested large amounts of egg white, even in instances when the urine contained small amounts of coagulable protein.

From our results it seems probable that the two tests although of the same general significance differ greatly in sensitivity, at least when applied to the identification of egg white in urine. The precipitin reaction is often positive in the presence of a negative anaphylactic test and it seems probable that the two reactions are not dependent absolutely on the same substances. This assumption is strengthened by the fact that the anaphylactic reaction was never positive in the absence of coagulable protein, which was not true of the precipitin test.[20]

III. TESTS FOR PROTECTIVE FERMENTS (ABDERHALDEN) IN BLOOD SERUM

The work of Abderhalden[21] and his co-workers is too well known to require any detailed description. In simplest form the theory is as follows: Foreign protein, when absorbed parenterally, stimulates the formation of certain protective substances which are capable of hydrolyzing this variety of protein. The claims of Abderhalden indicate that there is a great degree of specificity in the action of the antibody. The detection of such ferments is accomplished by digesting the suspected protein with the blood serum to be tested in a special dialyzing bag and

19. Wells, H. G.: Observations on Alimentary Albuminuria by Means of the Anaphylaxis Reaction, Jour. Am. Med. Assn., 1909, lii, 863.

20. This statement applies only to the identification of egg protein in the urine, for as stated previously, human urine which contains no coagulable protein may sensitize to human protein.

21. Abderhalden, E.: Der Nachweis blutfremden Stoffe, etc., Beitr. z. klin. Infectionskrank. u. Immunitätsforsch., 1913, i, 243 Abwehrfermente, Springer, Berlin, 1914.

TABLE 5.—INFANTS FREE FROM GASTRO-ENTERIC DISEASE

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1	5	10¾	—	One egg white, negative.....	29 and 32. Both negative to egg; 48 hours later negative to human serum	
2	6	12½	—	One egg white, negative.....	10. No reaction to egg; 48 hours later no reaction to human serum	
3	7	9½	—	One egg white, negative.....	.....	Had severe malnutrition. Recovery.
3, 1 week later	7	9⅞	—	Two egg whites + pure and 1-5		
4	6	11½	—	One egg white, negative.		
4, 1 week later	11	11⅞	—	Two egg whites, negative.....	.....	Developed intestinal disturbance 2 weeks later.
5	15	16 3/16	—	One egg white, negative.....	9 and 14. No reaction to egg; 72 hours later moderate reaction to human serum	Erysipelas 25 days later.
6	8	11½	—	One egg white, negative.....	54 and 56 . Negative to egg; moderate reaction to human serum 48 hours later	
7	9	14¾	—	Two egg whites + pure.....	89 and 91. Negative to egg; slight reaction to human serum 72 hours later	
7, 1 week later	9	14¾	—	One egg white, negative.		
8	13	16	—	Two egg whites, negative.		
9	24	—	—	Two egg whites, negative.		
10	24	—	—	One egg white, negative.		
11	24	—	—	One egg white, negative.		
12	6	11¼	—	Two egg whites, negative.....	18 and 26. Negative to egg white	
13	12	17¾	—	One and a half egg whites + pure, 1-5, 1-10	21 and 19. Negative to egg white; moderate reaction to human serum 48 hours later	
14	7	12 2/16	—	One and three-fourths egg whites, negative		

TABLE 6.—GASTRO-ENTERIC DISTURBANCE. MILD

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1	5	16	—	Two egg whites, positive; pure 1-5, 1-10	.....	Six to eight green, loose stools in 24 hours; slight loss of weight; no vomiting; temperature 100 to 101 F.
1, 3 days later	5	15 11/16	—	One egg white, negative.....	.....	Condition unchanged.
2	7	15	—	One egg white, negative.....	.....	Three to five greenish stools, mucus and soap curds; no fever or vomiting.
3	20	29¼	—	One egg white, positive; pure and 1-5	31 and 33. No reaction to egg.....	Three to six greenish, slightly loose stools; no fever or vomiting.
4*	6	11½	—	One egg white, negative.....	.....	Three to six greenish, slightly loose stools; no fever or vomiting.
5	16	19 6/16	—	One egg white, negative.....	.....	Three to six greenish, slightly loose stools; no fever or vomiting.
6	6	16	—	One egg white, negative.....	.....	Three to four slightly loose, yellow stools; mucus; no fever or vomiting.
7*	12	19½	—	One egg white, negative.....	4 and 9. No reaction to egg white; 48 hours later, slight reaction to human serum	Three to four slightly loose, yellow stools; mucus; no fever or vomiting.

* Suffered from malnutrition before onset of diarrhea.

TABLE 7.—GASTRO-ENTERIC DISTURBANCE. MODERATE

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1*	10	10	—	One egg white, negative.....	.....	Four to eight loose, yellow stools; mucus; temperature 100 to 102; slight prostration.
1, 2 days later	10	9 6/16	—	One and a half egg whites, positive; pure, 1-5, 1-10	.....	Four to eight loose, yellow stools; mucus; temperature 100 to 102; slight prostration.
2*	7	10	—	One egg white, positive; pure, 1-5, 1-10	36. No reaction to egg; 48 hours later, moderate reaction to human serum	Six to eight yellow, loose stools; mucus; blood; temperature, 100 to 101; vomiting.
3*	6	8	—	One egg white, negative.....	.....	Occasional vomiting; green, watery stools; temperature 100 to 102.
4	8	17	—	Albumin water as food. Ingested three to four egg whites in 24 hours; test, negative	.....	Day of onset, six watery, green stools; vomiting.
		16 11/16	Trace	Positive, pure, 1-5.....	32 and 35. Moderate symptoms to egg; 48 hours later, severe symptoms to human serum.	Second day, stools the same; no vomiting.
		16½	Moderate	Positive, pure, 1-5, 1-10, 1-50...	37 and 39. Severe symptoms to egg; 39, convulsions, died in one half hour; 37, recovery	Frequent green stools, loose; mucus and blood, fourth day.
		16 6/16	.....	No egg ingested for 48 hours; one and a half egg whites, test negative	.....	Eighth day, marked improvement.

* Suffered from malnutrition before onset of diarrhea.

TABLE 8.—GASTRO-ENTERIC DISTURBANCES. SEVERE

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1	14	16⅛	Trace	One egg white, negative.....	61 and 80. No reaction to egg white; severe reaction to human serum 48 hours later; 61 died in 20 minutes	*Albumin present independently of ingestion of egg.
1, 1 week later	14	15 5/16	Trace	Two egg whites, negative.....	1 and 5. No reaction to egg white; severe reaction to human serum	*Albumin present independently of ingestion of egg.
2†	13	11 6/16	Moderate	One egg white, negative.....	3 and 11. No reaction to egg white; severe reaction to human serum	*
2, 2 days later	13	10¾	Moderate	One egg white, positive pure, 1-10	.....	*
2, 6 days later	13	10 3/16	Moderate	Five-eighths egg white, positive pure, 1-5, 1-10, 1-50	100. Severe reaction; death in 40 minutes. 99. Moderate reaction; recovery; moderate reaction to human serum 62 hours later	Death 2 days later. Necropsy: enlargement and ulceration of lymphoid tissue of intestine.
3†	10	13½	Trace	One egg white, positive pure, 1-5, 1-10, 1-50, 1-100	82. Slight reaction; recovery. 89. Moderate reaction ; recovery. Both moderate reaction to human serum 3 days later	*Death 6 days after test.
4†	6	9	Heavy trace	Seven-eighths egg white, positive pure, 1-5, 1-10, 1-50	70. Death in 18 minutes. 76. Moderate reaction; recovery; moderate reaction to human serum 2 days later	*Death 9 days later.
5	7	16	—	One egg white, negative.....	.....	*Ill 2 days.
5, 2 days later	7	15 10/16	Trace	One egg white, positive pure, 1-5	18 and 24. Moderate reaction to egg	
5, 4 days later	7	15 1/16	Trace	One egg white, positive pure, 1-5, 1-10, 1-50	.....	Death 4 days later.
6	7	15	Trace	One egg white, positive pure, 1-5, 1-10, 1-50	18 and 24. Moderate reaction to egg	*

* Severe general disturbances; frequent watery stools; vomiting; prostration.
† Malnutrition before onset of gastro-enteritis.

TABLE 9.—Infantile Eczema

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1*	3	12	Trace	One egg white, positive pure, 1-5 and 1-10	.....	Severe eczema face, neck and arms.
2*	4	12¾	—	One egg white, negative.....	93 and 97. No reaction to egg.....	Seborrheic eczema of scalp.
3*	4	13	Moderate trace	One egg white, positive pure, 1-5	10 and 6. Moderate reaction to egg; severe reaction to human serum	Eczema of face, chest and arms.
4	6	15½	Trace	One egg white, negative.....	.....	Eczema of face, chest and arms.
5*	6	16	Trace	One egg white, positive pure and 1-5	51 and 57. Slight reaction to egg.....	Eczema of buttocks, abdomen, scalp and face.
6	7	15¾	—	One egg white, negative.....	.....	Eczema of face and scalp.

* Developed urticaria after ingestion of egg.

TABLE 10.—MALNUTRITION ATROPHY

Number	Age, Months	Weight, Pounds	Albuminuria	Precipitin Test	Anaphylactic Test	Remarks
1	3¼	4¾	Very faint trace	One egg, positive pure, 1-5, 1-10, 1-50	.....	Marasmus ?.
2	1	5⅝	Faint trace	One egg, negative.....	.....	Albuminuria not dependent on ingestion of egg.
3	6	6¾	Faint trace	One egg, negative.....	.....	Albuminuria not dependent on ingestion of egg. Marasmus.
4	7	8	—	One egg, positive pure.....	7. Negative	Marasmus.
5	1½	6	—	One egg, positive pure, 1-5, 1-10		
6	2	6	—	One egg, positive pure.		
7	2	6 5/16	Faint trace	Two eggs, positive pure, 1-5, 1-10	98 and 96. No reaction to egg; 24 hours later, moderate reaction to human serum	
7, 2 weeks later	2½	6 5/16	—	One egg, negative.		
8	4	8½	Moderate trace	Two eggs, positive pure, 1-5, 1-10, 1-50	46 and 47. Severe reaction. 46. Death in convulsions in 20 minutes. 47. Recovered.	
8, 2 weeks later	4½	8½	—	One egg, negative.		
9	3	7¾	—	Two egg whites, negative.....	97. Negative; 29 hours later, marked reaction to human serum.	
9, 2 weeks later	3½	7½	—	Two egg whites, negative.		
10	24	17¼	—	One egg white, negative.....	21 and 22. Both negative to egg white; slight reaction to human serum 48 hours later	Moderate rickets.
10, 2 days later	24	17¼	—	Two egg whites, positive pure, 1-5		
11	16	17	Faint trace	One egg white, positive pure, 1-5, 1-10	2 and 5. Slight reaction to egg. .	
12	16	18¾	Faint trace	One egg white, positive pure, 1-5	70 and 71. Severe reaction to egg; 48 hours later, moderate reaction to human serum	Otitis media. Rickets.
13	12	17 8/10	—	One egg white, positive pure, 1-5		
14	24	....	—	One egg white, positive pure, 1-5	91 and 92. No reaction to egg; 36 hours later, slight reaction to human serum	Pertussis. Rickets.
15	8	11½	Trace	Two egg whites, positive pure, 1-5	68. Slight (?) reaction to egg; 3 days later, moderate reaction to human serum	Rickets.
16	9	15⅛	Trace	Two egg whites, positive pure, 1-5, 1-10, 1-50	83. Severe reaction to egg; death in 30 minutes. 89. Moderate reaction to human serum; 28 hours later, moderate reaction to egg white	Otitis media.

testing the dialysate for protein cleavage products. Properly controlled, a positive reaction should indicate the presence of a proteolytic ferment in the serum capable of digesting the protein used.

Assuming that the contentions of Abderhalden and his co-workers are correct, the presence of a protease capable of digesting milk in the blood serum of nurslings would indicate that undigested milk protein had been absorbed and had provoked the formation of protective ferments. It was with this hypothesis in mind that we used the test.

Technic.—The procedure of Abderhalden was carefully followed. Milk and egg protein, coagulated by heat and acetic acid, were carefully washed until free from substances capable of giving a positive ninhydrin reaction. These proteins were kept on ice in chloroform water and were tested from time to time to exclude the formation of dialyzable products.

The special dialysis bags of Schleicher and Schüll were used and each bag was tested (1) to show that it was permeable to silk peptone, and (2) that it was not permeable to the coagulated protein preparations. After use the bags were treated with boiling water and kept in sterile water under toluene. Before further use, each was again tested as mentioned above.[22]

The serum was collected in the usual way and all specimens tinged to the slightest degree, with blood, were discarded. Two control tests were made with each experiment: (1) The serum heated to destroy any ferment present was dialyzed with the protein to be tested; (2) the fresh serum was dialyzed alone. Such tests should be negative.

The only departure from the technic advised by Abderhalden was the use of 0.8 c.c. instead of 1.5 c.c. of serum. This was necessitated by the smaller amounts of blood obtainable from infants.

DISCUSSION OF RESULTS

The results of the tests are shown in Tables 11 to 15, inclusive. The reaction was present often in apparently normal infants and children. It was present with greatest frequency in cases of chronic malnutrition and subacute intestinal disorders. Of interest is the fact that the serum of several infants who had never eaten egg contained a ferment capable of digesting egg protein. This finding is very difficult to explain on the basis of Abderhalden's hypothesis.

In the present state of our knowledge, a discussion of these results with any degree of assurance is impossible. Granting the correctness of Abderhalden's views, the positive tests indicate an absorption of undigested protein and have the same significance as the anaphylactic or precipitin reactions. His views, however, have not been generally accepted and there is an enormous controversial literature which it is beyond the scope of this paper to discuss. Since, therefore, the origin and function of a proteolytic ferment in the blood serum is a mooted

22. It is worthy of note that the unreliability of the dialysis bags was a tremendous obstacle in the work. A large percentage were found useless on the first tests and after use a considerable number became impermeable to peptone or permeable to the coagulated protein.

TABLE 11.—Tests for Protease in Blood Serum of Apparently Normal Infants and Children

No.	Age, Months	Weight, Pounds	Protease Serum		Remarks
			Milk	Egg	
1	2	10	—	—	
2	3	11	+	..	
3	3	12	—	—	
4	4	12½	—	+	Had never eaten egg; cutaneous test neg.
5	6	16	+	—	
6	6	15	+	+	Had never eaten egg; cutaneous test neg.
7	6	14	—	..	
8	6	15	—	..	
9	7	15½	—	—	
10	8	17½	+	+	
11	10	16	—	—	
12	18	19½	—	+	
13	18	22	—	—	
14	24	24	—	+	
15	30	24½	+	—	
16	36	23	—	—	
17	36	24	—	—	
18	42	23½	+	—	
19	42	30	—	+	
20	48	32	—	—	

TABLE 12.—Tests for Protease in the Blood Serum of Infants Affected with Eczema

No.	Age, Months	Weight, Pounds	Protease Serum		Remarks
			Milk	Egg	
1	5	12	+	+	Had never eaten egg; cutaneous test +
2	5	13	—	—	
3	5	12½	—	+	Had never eaten egg; cutaneous test +
4	5	14	+	—	
5	6	14½	—	—	
6	6	16	+	+	Cutaneous test +
7	6	15	—	+	Cutaneous test —
8	6	15½	+	+	Cutaneous test —
9	6	14½	+	—	
10	7	16	—	+	Cutaneous test —
11	7	18	+	+	Cutaneous test —
12	7	17½	—	+	Cutaneous test +
13	8	16	+	+	
14	9	17	—	—	

TABLE 13.—Tests for Protease in the Blood Serum of Infants Suffering from Chronic Malnutrition

Number	Age, Months	Weight, Pounds	Protease Milk	Number	Age, Months	Weight, Pounds	Protease Milk
1	4	7¾	+	10	7	9¼	+
2	4	8	+	11	8	10½	+
3	5	9	—	12	8	10¼	—
4	5	10	+	13	8	11	+
5	6	10½	+	14	9	11½	—
6	6	11	—	15	10	12½	+
7	6	11½	—	16	10	11	+
8	7	9½	+	17	12	10½	—
9	7	10	+				

TABLE 14.—Subacute Intestinal Disturbances

Number	Age, Months	Weight, Pounds	Protease Milk	Number	Age, Months	Weight, Pounds	Protease Milk
1	3	10	+	10	7	14½	+
2	3	9	+	11	7	12½	+
3	5	14	+	12	7	14	+
4	5½	13½	—	13	8	13	+
5	6	14	—	14	8	15½	—
6	6	13	+	15	9	15	+
7	6	12½	+	16	10	13	—
8	7	14	+	17	10	14	+
9	7	13½	+				

TABLE 15.—Acute Intestinal Disturbances

Number	Age, Months	Weight, Pounds	Protease Milk	Number	Age, Months	Weight, Pounds	Protease Milk
1	4	11¾	—	7	8	16	—
2	6	13½	—	8	8	13½	+
3	6	14	+	9	10	14½	—
4	7	15	—	10	11	14½	—
5	7	15½	—	11	13	15½	+
6	7	14	+				

question, an attempt to attach any definite significance to its presence would savor too strongly of speculation to be profitable.

IV. SUMMARY AND CONCLUSIONS

As shown by precipitin and anaphylactic tests applied to the urine, the intestinal tract of normal infants is usually impermeable to undigested foreign protein.

In nutritional or gastro-enteric disorders, foreign protein may be absorbed in an undigested or partially digested state and appear in the urine.

The precipitin reaction, applied to the urine for the detection of egg protein, is apparently more delicate than the anaphylactic test.

These results demonstrate the possibility that certain nutritional disorders in artificially fed infants may be due to the biologic character of the food, although they obviously give no direct evidence to support such a view.

We are greatly indebted to Professor Gies for placing the facilities of his laboratory at our disposal, and to him and his associates for much assistance.

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EXPERIENCES WITH ETHYLHYDROCUPREIN IN THE TREATMENT OF MEASLES, SCARLET FEVER AND OTHER INFECTIONS *

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MINNEAPOLIS

The studies of Morgenroth and his collaborators have shown that a number of quinin derivations manifest considerable curative powers against trypanosomes, spirochetes and pneumococci, and that this power reaches its maximum in the substance known as ethylhydrocuprein.

Although this drug is very successful in curing mice affected with pneumococcus septicemia, Engwer and also one of us (H.) have been unable to obtain any striking series of cures in guinea-pigs and rabbits with experimental lobar pneumonia, even with the lowest dose (60,000 pairs per cubic millimeter) which is certainly fatal.

This drug has been used with a certain amount of success in clinical pneumonia by Linné and Vetlesen and also locally in cases of pneumococcus keratitis by Ginsberg. Giemsa and Izar have found it a specific in the treatment of stubborn estivo-autumnal malaria cases which have withstood the action of quinin.

Further extension of clinical observation with this drug in other infectious diseases was warranted; and we made tests on cases of measles and scarlet fever, using a supply of ethylhydrocuprein which had been kindly furnished to one of us by Professor Morgenroth. Our observations on scarlet fever gave negative results. Cases occurring in the contagious service of the Minneapolis City Hospital and in the private practice of one of us (S.) were treated with ethylhydrocuprein in capsules in doses of 0.1 to 0.5 gm. three times a day, according to the age of the patient. No cinchonism or other deleterious symptoms were manifested in our series. On the other hand, no beneficial effects were apparent in this series, for in the seven treated cases, the fever and acute symptoms showed an average duration of 8.9 days, while in the seven untreated cases occurring at the same time in the same hospital and in the same private practice, the average duration was 7.4 days (see Tables 1 and 2).

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In measles, however, the effects seem more promising. Eleven unselected cases were treated (Table 3) and showed an average duration of 4.3 days, while among ten unselected cases (Table 4) occurring

TABLE 1.—SCARLET FEVER, ETHYLHYDROCUPREIN SERIES

No.	Name	Age	Duration of Fever (Days)*		Max. Temp.	Principal Symptoms
			Total	After E.H.C.		
1	Rose T.	4	12	6	103.4	Red rash over entire body. Sore throat. Acute rhinitis
2	Barty F.	7	9	7	103	Severe inflammation of throat. Rash disappeared on fourth day
3	Max T.	7	10	8	104	Eruption extensive. Sensorium clear. Throat inflamed. No rash visible on fourth day. Slight dry cough
4	Gladys B. ...	20	8	6	104	Rash over entire body. Throat inflamed. Sensorium clear. Eruption disappeared on third day
5	Willis R.	16	7	5	104	Headache. Sore throat. Enlarged glands
6	Pearl G.	31	8	6	102	Sore throat. Nausea. Pronounced angina. Enlarged glands
7	Selma R.	25	8	5	101.5	Sore throat. Headache. Nausea. Membranous exudate.

* Average duration 8.9 days. After ethylhydrocuprein, 6.1 days.

TABLE 2.—SCARLET FEVER, CONTROL SERIES

No.	Name	Age	Duration of Fever (Days)*	Max. Temp.	Principal Symptoms
1	Gustaf C. ...	22	4	99.5	
2	Olga A.	9	5	102	
3	Leonia B. ...	29	7	104	Pain in wrists, then in entire body. Swelling of ankles. Epithelium in urine
4	Ellen D.	23	7	101.2	Slight epistaxis. Urine negative
5	Lillie G.	16	8	103	Pain in abdomen. Calcium oxalate in urine
6	Louis B.	7	12	103.5	Rash over entire body. Abdomen slightly distended. Throat culture negative. Triple amorphous phosphates in urine. Also urates.
7	Alex H.	19	9	104.5	Nausea. Sore throat and delirium. Eruption faded on sixth day. Urine negative
	* Average duration 7.4 days.				
	Complications—				
8	Bertha B. ...	19	12	104.5	Sore throat. Delirium. Diagnosis: scarlet fever and diphtheria
9	Marie E.	26	10	104.5	Sore throat. Delirium. Right eye discharging. Hyaline casts in urine. Diagnosis: scarlet fever and diphtheria
10	Agnes A.	23	4	101	Cough. B. B. C., triple phosphates and amorphous urates in urine. Diagnosis: scarlet fever and diphtheria

under the same circumstances and during the same months of the same year, the average duration was 7.9 days. Moreover, all the treated cases were free from complications, while in the untreated

there were six cases of severe complications among sixteen consecutive cases in the Minneapolis City Hospital (Table 5), which materially lengthen the average duration of a larger series of untreated cases.

TABLE 3.—MEASLES, ETHYLHYDROCUPREIN SERIES

No.	Name	Age	Duration of Fever (Days)*		Max. Temp.	Principal Symptoms
			Total	After E.H.C.		
1	Isaac T.....	5	5	5	104.8	Sore throat. Coryza. Photophobia. Slight bronchitis. Delirium.
2	Gertrude T...	7	5	3†	104.4	Sore throat. Tonsillitis. Face swollen. lacrimation
3	Mrs. H. N. ...	27	5	2	103.5	Marked coryza and lacrimation. Urine negative at all times
4	Madeline K. .	4	4	2	103	Coryza. Lacrimation. Photophobia. Bronchitis. Urine negative
5	Freddie W. ..	5	5	4	103.8	Convalescing from scarlet fever. Cough. Delirium. Hyaline and granular casts in urine first day
6	Rena H.....	24	4	3‡	105	Headache and cough
7	Jerome J.	9	4	2	104.5	Itching of eyes and coryza. Photophobia
8	Helen V.	10	2	1	104	Itching of eyes and coryza. Cough
9	Willard L. ...	5	4	3§	104	Face swollen. Coryza. Photophobia
10	Ethel S.¶.....	19	6	2‖	104.8	Face swollen. Severe cough. Photophobia
11	Milda H.	22	3	..	100.5	Symptomatic scarlet fever

* Average duration 4.3 days. Average duration after ethylhydrocuprein 2.6 days.
† Pneumonia. ‡ Bronchitis. § Diphtheria. ‖ Convalescing scarlet fever.
¶ Slow beginning fever. No typical signs until the fifth day. Treatment followed by very prompt improvement.

TABLE 4.—MEASLES, CONTROL SERIES, JANUARY, 1913, TO JANUARY, 1914

No.	Name	Age	Duration of Fever (Days)	Max. Temp.	Principal Symptoms
1	Joe T.....	29	4	102	Cough, nausea and rash the first day. Cough continued till fourth day
2	Sophy H.	22	9	104	
3	Charles K. ...	22	10	103	Cough throughout the period of temperature
4	Albin B.....	26	3	102.6	
5	Carrie W. ...	24	3	100.2	Cough developed simultaneously with rash
6	John K.....	22	5	103	Sore throat. Cough
7	Lizzie M.	30	6	102.4	Severe cough. Rash faded on fourth day
8	Victor E.	21	3	102.6	Sore throat. Cough. Cough subsided on the third day
9	Sam S.	23	3	102.4	Cough and considerable rash

In striking contrast to these cases, one of the treated patients escaped from the hospital and on being returned to the hospital after some hours' exposure showed definite signs of beginning lobar pneumonia; but these signs retrogressed and cleared up within twenty-four hours.

It cannot be stated, however, that all the results were unequivocally favorable to the idea that ethylhydrocuprein might prove a specific for the treatment of measles. The duration of the eruption was utterly unaffected by the treatment. One child (I. T.), whose sister had already been receiving ethylhydrocuprein for severe measles, became ill and was given ethylhydrocuprein by mistake by his mother at the

TABLE 5.—MEASLES, CONTROL SERIES, APRIL TO JULY, 1914

No.	Name	Age	Duration of Fever (Days)*	Max. Temp.	Principal Symptoms
1	Leroy C.	24	9	104	Coryza. Lacrimation. Slight bronchitis. Urine negative
2	Jennie L.	19	7	103	Pronounced photophobia. Urine negative
3	Paul R.	5	5†	104	Photophobia. Somnolence and some delirium
4	E. R. G.	21	10	105	Nose bleed. Sore throat. Pains in chest. Considerable coughing
5	Ed. M.	50	9	102.2	Cough. Nausea. Hiccoughs. Rash over entire body
6	Wm. H.	35	9	102.5	Rash over entire body. Urine negative
7	Lillie L.	22	8	104.5	Hard cough. Sore throat. Hoarseness. Urine negative
8	Marie H.	23	6	105	Severe headache. Sore throat. Cough. Expectorates thick yellow mucus. Pain and distention of abdomen
9	Lillian S.	21	5	100	
10	Ruth N.	25	14	103.2	Severe cough throughout course
* Average duration 7.9 days.					
Complications—					
11	Mrs. W. M. B.	22	7	102.5	Diagnosis: scarlet fever, diphtheria, measles
12	Floyd B.	17	17	104.5	Sore throat; chills. Diagnosis: scarlet fever, measles
13	Arthur P. ...	21	21	104.7	Headache, cough, nausea. Diagnosis: scalet fever, diphtheria and measles
14	Eleanor E. ..	4	6‡	103	Earache. Coryza. Cough. Diagnosis: mastoiditis, bronchitis
15	Mrs. S. E. ...	40	3§	100	Very stupid; restraint necessary. Involuntary voiding of urine. Albumin, casts and pus cells in urine. Diagnosis: scarlet fever, diphtheria, measles
16	Chester I. ...	7	15¶	103.5	Rash on face and neck only. Pronounced coryza; eyes swollen; inflamed throat and cough. Diagnosis: pleural pneumonia, measles

† Hemorrhagic type. ‡ Mastoiditis and bronchitis. § Scarlet fever, diphtheria, measles. ¶ Pleural pneumonia, measles.

first outbreak of symptoms. In spite of this early treatment, which was continued throughout the febrile period, his illness was of moderately severe grade, his fever lasted five days, and his eruption and other symptoms were in no wise mitigated. In most of the cases, however, the fever fell and toxic symptoms abated markedly soon after the installation of treatment.

The series of cases treated thus far is too limited to warrant the drawing of conclusions,[1] but in view of the difficulty of obtaining a sufficient supply of the drug under present European conditions, it has seemed to us worthy of being placed on record as a preliminary publication; it indicates that ethylhydrocuprein is worthy of further trial in the treatment of measles.

The experiments of Valenti and of Moon on the favorable effects of quinin in rabies made it seem possible that ethylhydrocuprein might prove of value in this and in other infections due to filterable viruses. One of us has tried it in experimental rabies (in collaboration with Dr. McDaniell of the Minnesota Public Health Service), experimental vaccinia, and in collaboration with Drs. Herman Binger and Murray (Minneapolis), in a few cases of trachoma. In all these conditions, however, no effect was noted.

Morgenroth, J., and Halberstaedter, L.: Zur Kenntnis der Chininwirkung, Berl. klin. Wchnschr., 1910, xlvii, 646; Ueber die Heilwirkung von Chininderivaten bei experimenteller Trypanosomeninfektion, ibid., 1911, lviii, 1558.

Morgenroth, J., and Levy, R.: Chemotherapie der Pneumokkeninfection, ibid., 1911, xlviii, 1560, 1979.

Morgenroth, J., and Kaufmann, M.: Zur Chemotherapie der experimentellen Pneumokokkeninfektion, Zentralbl. f. Bakteriol., 1912, liv, Ref. Beilage 69.

Gutmann, L.: Zur experimentellen Chemotherapie der Pneumokokkeninfektion, Ztschr. f. Immunitätsforsch., 1912, xv, 625.

Rosenthal, F., and Orien: Zur experimentellen Chemotherapie der Pneumokokkeninfektion, ibid., 1914, xx, 572.

Rosenthal, F.: Zur Chemotherapie der Experimentellen Pneumokokkeninfektion, Berl. klin. Wchnschr., 1914, li, 573.

Hirschfelder, A. D.: Unpublished experiments.

Vetlesen, H. J.: Ueber die chemotherapeutische Behandlung einiger Fälle von Pneumonie mit Aethylhydrocuprein, Berl. klin. Wchnschr., 1913, l, 1473.

Lenné: Zur Behandlung der Pneumonie mit Aethylhydrocuprein und Pneumokokkenserum, ibid., 1913, i, 1976.

Ginsberg, S., and Kaufmann, M.: Beeinflussung der kornealen Pneumokokkeninfektion beim Kaninchen durch Chinaalkaloide, Klin. Monatsbl. f. Augenh., 1913, N. F., xv, 804.

Goldschmidt, M.: Zur Spezifischen Therapie der Pneumokkeninfektion des menschlichen Auges, besonders des Ulcus corneae serpens, durch Aethylhydrocuprein, ibid., 1913, N. F., xvi, 449.

Giemsa, G., and Werner, H.: Erfahrungen mit Weiterem dem Chinin nähestehenden Alkaloiden und einigen ihrer Derivate bei Malaria, Beihefte z. Arch. f. Schiffs und Tropenhygiene, 1914, xviii, 81.

Izar, G., and Nicosia, R.: Ueber Chemotherapie bei Malaria, Berl. klin. Wchnschr., 1914, li, 385.

Valenti, A.: Azione della chinine sul virus rabido, Boll. Soc. Med. e Chir. di Pavia, 1904, iv, 38.

1. Experimental measles has been produced in the monkey by Anderson and Goldberger, but Professor Anderson has assured us that in this animal the disease is too mild and the infection too uncertain to furnish as satisfactory evidence of therapeutic results as can be obtained in the clinic.

Moon, V. H.: The Effect of Quinin on Rabies in Dogs, Jour. Infect. Dis., 1913, xiii, 165. Since this article was written there have appeared also:

Frothingham, L., and Halliday, J.: Effect of Quinin on Rabbits Inoculated with Rabies, Jour. Infect. Dis., 1914, xxx, 275.

Krumwiede, C., and Mann, A. G.: The Effect of Quinin in Rabies, Jour. Infect. Dis., 1915, xvi, 24.

Moon, V. H.: Further Observations on the Effects of Quinin in Rabies, ibid., 1915, xvi, 58, which contradict Moon's first observations.

REPORT OF A CASE OF PROLONGED ANURIA WITH FEW SYMPTOMS *

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LEAD, S. D.

Mamie R., 7 years old. Premature at 6½ months, raised in an incubator and fed on malted milk. Teething was normal. She walked at 13 months, but was always a tiny baby. She was never sick during childhood, but was always delicate.

On March 3, 1914, she was taken with an attack of scarlet fever, so mild that it would have been overlooked, but for the fact that another more marked case appeared in the same family. All during the attack she passed but little urine, an average of 1½ ounces daily. On March 23 she came under my care. Physical examination at that time was negative; there was no edema nor symptoms of any description except the scanty urine. Mentally she was very bright, and continued so throughout the time reported on. The child was very thin and it was possible to palpate the entire abdomen thoroughly.

The following table represents the actual amount of urine passed over a prolonged period:

Date	Ounces	Date	Ounces
March 23	1½	April 22	4
March 29	3	April 24	2
March 31	2½	April 26	3
April 3	30	April 27	1
April 5	3	April 28	3
April 6	1¾	April 29	4
April 7	3	May 1	1½
April 8	4	May 3	3
April 9	2	May 5	3
April 12	2	May 6	3
April 15	1¾	May 7	3
April 16	2½	May 8	*
April 17	½	May 9	8
April 19	3		

* Profuse.

From this time on the amount increased very rapidly and by the end of the following week had reached normal. On only one examination were any casts found, and then two granulars appeared. No albumin was ever detected.

This was an extremely interesting case, because the anuria seemed to have no influence on the patient's condition. At only one time did she have a convulsion and then it was not very severe. The parents of this child were very intelligent, and I am positive they did not overlook the least amount of urine passed.

When the amount on April 3 jumped to 30 ounces, we were satisfied that she had a retention, but we are of the opinion now that subsequent events showed this not to be the case. All kinds of treatment were tried: the salt-free diet, the Fischer hypertonic salt treatment, and the use of thyroid, diuretics, hot packs, etc., the only demonstrable results being no change for the worse.

The little girl was in perfect health soon after these data were compileu, and has remained so ever since. Repeated examinations of the urine in the last two years have failed to find anything pathologic.

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PROGRESS IN PEDIATRICS

REVIEW OF NEUROLOGY IN CHILDHOOD FOR 1914-1915

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CEREBROSPINAL FLUID

The latest conception regarding the manner of formation of cerebrospinal fluid is that it is a product of the secretory activity of the epithelium of the choroid plexus. Drugs which stimulate glandular secretion are supposed to increase the formation of cerebrospinal fluid. Using chlorbutanol as an anesthetic, Dandy and Blackfan[1] trephined the Atlas and inserted a special fitting cannula. The animal was so placed that the cannula formed the dependent part. A steady outflow of cerebrospinal fluid was thus obtained, after allowing the accumulated fluid to escape. Jugular compression, by production of cerebral venous stasis, caused an instantaneous increase of cerebrospinal fluid. Ether also caused an increased production of fluid. Amyl nitrite had no such effect. Pilocarpin produced a constant but very slight increase. Intravenous injections of freshly prepared aqueous extracts of choroid plexus and of posterior lobe of pituitary body failed to produce any increase. Following the pilocarpin experiments, the choroid plexuses were removed for histological study. No alterations which could be ascribed to glandular activity were observed.

"One of the strongest arguments in favor of the secretory theory of cerebrospinal fluid formation is the difficulty with which foreign substances pass from the blood to the cerebrospinal fluid." Of several substances tried, hexamethylenamin and salicylic acid were the only substances which Dandy and Blackfan could demonstrate in the spinal fluid after oral, subcutaneous and intravenous administration. Flooding the blood with colored solutions, such as indigo, carmin, trypan blue, and phenolsulphonephthalein failed to show even a trace in the cerebrospinal fluid. These investigators further state:

"The behavior of the Wassermann reaction in the cerebrospinal fluid of hereditary syphilis, without involvement of the central nervous system, gives further evidence of the impermeability of the choroid plexus to foreign substances. In the majority of patients whom we

1. Dandy, W. E., and Blackfan, K. D.: Am. Jour. Dis. Child., 1914, viii, 406.

examined, the reaction was positive in the blood, but in no instance was there a positive reaction in the cerebrospinal fluid." Summarizing the views on the production of cerebrospinal fluid, they think probable that "cerebrospinal fluid is formed both by filtration and secretion."

Dandy and Blackfan studied the absorption of cerebrospinal fluid by substituting phenolsulphonephthalein solution for cerebrospinal fluid. The excretion of the dye was determined in the urine, blood and lymph. It was detected in the blood in three minutes, whereas there was no trace in the lymph for forty-five minutes. It appeared in the urine in five minutes. The greatest amount of absorption occurs from the spinal subarachnoid space, there being practically no absorption from the ventricles.

They were unable to find evidence supporting the existence of stomata in the subarachnoid space. India ink and lamp black granules substituted for cerebrospinal fluid, even when injected under a pressure of 100 mm., failed to show any passage of granules into the blood.

Grulee and Moody[2] take exception to the statement made by Miller and Levy that the Lange "gold chlorid reaction has no advantages over known laboratory proceedings in the diagnosis of congenital syphilis." They obtained characteristic reactions in the 1 to 40 and 1 to 80 dilutions in eighteen cases of congenital syphilis. In meningitis, reactions occur in the higher dilutions.

"Brain tumors, toxic meningitis (meningismus), edema from sunstroke, uremia, etc., may give a slight reaction in the fourth, fifth and sixth tubes (1 to 80, 1 to 60 and 1 to 320) when they react at all. The reactions in this group are rarely stronger than a dark blue and usually lie between a red blue and a violet."

Neisser and Friedman had previously shown that other inorganic colloids besides gold chlorid could be used in the same manner. Emanuel[3] adopted a Mastix solution, which is easily prepared. Five tubes are used for the test. In the first tube 1.5 c.c. of a 1.25 per cent. salt solution is placed. Only 1 c.c. is put in the other tubes. To the first tube, 0.5 c.c. of spinal fluid is added. After thoroughly mixing, 1 c.c. of the mixture in the first tube is added to the second, 1 c.c. of the second to the third, and so on. None of the mixture is put in the fifth tube. One c.c. of the Mastix solution is added to each tube. The reaction is read at the end of twelve hours. With normal spinal fluids, no precipitation occurs in the first four tubes, indicating the presence of a protective colloid. In syphilis of the brain and tabes, precipitation occurs in all five tubes.

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2. Grulee, C. G., and Moody, A. M.: Am. Jour. Dis. Child., 1915, ix, 17.
3. Emanuel, G.: Berl. klin. Wchnschr., 1915, lii, 793.

Major and Nobel[4] find the glycyl tryptophan reaction a valuable addition to the diagnostic measures used in meningitis. The test determines the peptolytic power of cerebrospinal fluid. In no case without meningitis did these observers obtain a positive reaction. Various dilutions, up to 1 to 200, are made. One c.c. each of the fluid and glycyl tryptophan are placed in a test tube, and 1 c.c. toluene added as a preservative. The mixture is incubated for three hours. A few drops of dilute acetic acid are added, and then a small amount of oversaturated calcium chlorid, to be briskly shaken just before using. In the presence of free tryptophan a red color is obtained.

Segagni[5] found the test constantly negative in eight cases of tuberculous meningitis, one of cerebral hemorrhage, and one of cerebellar tumor.

The value of the Meyerhofer test for spinal fluid is confirmed by Lackner and Levinson.[6] The test consists in determining the amount of decinormal permanganate solution reduced by 1 c.c. of cerebrospinal fluid when boiled for ten minutes in a strongly acid medium.

Lemchen[7] describes a new method of staining cells in the cerebrospinal fluid. Two solutions are prepared. Solution 1 is 2 per cent. benzidin in glacial acetic acid. Solution 2 is hydrogen peroxid. The two solutions are mixed in a small test tube before using. A white cell pipet is used to make the dilution. "Draw the stain to 0.5 and spinal fluid to 11. Mix and count." Red blood cells are stained blue, polymorphonuclears are stained light yellow, while the nucleus is visible by having blue granules in it. In lymphocytes the periphery is stained, appearing as a dark-blue ring.

The reduction of Fehling's solution in the cerebrospinal fluid has been utilized for diagnostic and prognostic purposes. DuBois and Neal[8] state that while the absence of reduction is of marked significance, its presence means nothing. Equal quantities of cerebrospinal fluid and Fehling's solution should be used. These observers obtained reduction in 73 per cent. of tuberculous fluids. Abramson[9] thinks the test has definite prognostic value not only in poliomyelitis but in other pathologic conditions. "A fluid that does not reduce Fehling's solution indicates an extensive and severe pathologic change." When the reducing power returns, improvement follows.

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4. Major, R. H., and Nobel, E.: Arch. Int. Med., 1914, xiv, 383.
5. Segagni, S.: LaPediatria, 1914, xvii, No. 12.; abstr., Jour. Am. Med. Assn., 1915, lxiv, 285.
6. Lackner, E., and Levinson, A.: Arch. Pediat., 1915, xxxii, 508.
7. Lemchen, B.: Med. Rec., New York, 1915, lxxxviii, 443.
8. DuBois, P. L., and Neal, J. B.: Am. Jour. Dis. Child., 1915, ix, 1.
9. Abramson, H. L.: Am. Jour. Dis. Child., 1915, x, 344.

Auer[10] studied the functional effect of experimental intraspinal injections of serums with and without preservatives. He endeavored thereby to determine the explanation for the occasional fatalities following the use of antimeningitis serum. Auer shows that one of the main dangers seems to be the increased intraspinal pressure, as has been suggested by Flexner. That this factor of increased pressure is a prominent one, is shown by the injection of a few cubic centimeters of tricresol serum after the previous introduction of plain horse serum. A stoppage of respiration, broken occasionally by short gasps, occurs; a profound drop in blood pressure, and a marked slowing of the pulse. The removal of spinal fluid in such an instance suffices to restore pulse, blood pressure and respiration to their normal condition. Auer recommends that one be prepared to remove part of the injected fluid, and to administer artificial respiration. He suggests the use of a preservative which could be removed just before injection. Ether seems preferable to chloroform.

DuBois and Neal also think that the cause of fatalities following intraspinal injection of serum is probably "due to injudicious administration of the serum—too large dose, or too rapid increase of pressure, which is likely to happen unless the gravity method is used—or to an unusual susceptibility on the part of the patient." They also note that similar fatalities have been reported from France, "where serum without preservative is used."

Fonzo[11] records the occurrence of a respiratory failure during lumbar puncture which was performed on a child with meningitis. He explains the death by a probable "hyperemia ex vacuo" in the bulbar region. In order to facilitate the entrance of the trocar, the head was strongly flexed forward, probably causing a sudden displacement of cerebrospinal fluid forward.

Quincke[12] discusses the various indications for lumbar puncture. In acute cases of serous meningitis, lumbar puncture may effect a cure. Brain tumor is no contraindication for lumbar puncture. On the contrary, if carefully done, it may be beneficial, even causing a subsidence of choked disk.

Smith[13] and Lapage[14] report their experiences with lumbar puncture in the diagnosis and treatment of nervous diseases in childhood.

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10. Auer, J.: Jour. Exper. Med., 1915, xxi, 43.
11. Fonzo, F.: LaPediatria, 1914, xxii, 286.
12. Quincke, H.: Therap. Monatsh., 1914, xxviii, 469.
13. Smith, F. H.: South. Med. Jour., 1915, viii, 858.
14. Lapage, C. P.: Med. Chron., 1914, xxvii, 227.

MENINGITIS

Bardth[15] recommends the surgical treatment of purulent meningitis by lumbar laminectomy and drainage of the dural sac. The usual picture of meningitis observed at necropsy has made us skeptical in regard to the probable usefulness of any surgical measures. Bardth reminds us that a similar line of reasoning prevented us heretofore from treating peritonitis surgically.

Despite the bad results thus far obtained by drainage of the cisterna magna, Kopetzky[16] believes that in purulent meningitis such an operation may prove a useful measure. He urges that the operation should not be entirely discarded.

Leighton and Pringle[17] report two cured cases of streptococcus meningitis, treated surgically. One of these was in a child, aged 8 years. Lumbar laminectomy over the third lumbar vertebra was followed by complete recovery.

DuBois and Neal,[18] reporting a complete recovery from streptococcus meningitis, disapprove of operative measures and think that Haynes' advice to operate on all patients with septic meningitis is quite unjustifiable.

Herman[19] reports a case of pneumococcus meningitis in a sixteen-day-old infant. It was admitted to the hospital with a subnormal temperature. The physical examination was negative. Death occurred after twenty-four hours. A necropsy showed the presence of pneumococcus meningitis.

Mauriac and Philip[20] report a case of pneumococcus meningitis which developed one month after scarlet fever. The child, 8½ years old, was taken sick with vomiting and epileptiform movements of the left side, followed by fever and coma. The urine contained a large amount of albumin, the blood and spinal fluid a large amount of urea. The second lumbar puncture revealed a pneumococcus meningitis.

Krever[21] distinguishes two forms of pneumococcus meningitis, differing in their origin and prognosis. The variety complicating a pneumonia is more fatal than that following nasopharyngitis.

Favorable results obtained by the use of ethylhydrocuprein in various pneumococcus infections have been reported by numerous observers during the past eighteen months. From the neurological viewpoint, it is encouraging to read of even a rare cured case of pneumococcus meningitis.

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15. Bardth: Arch. f. klin. Chir., 1914, cv, 653.
16. Kopetsky, S. J. Laryngoscope, 1914, xxiv, 733.
17. Leighton, W. E., and Pringle, J. A.: Jour. Am. Med. Assn., 1915, lxiv, 2054.
18. DuBois, P. L., and Neal, J. B.: Arch. Pediat., 1915, xxxii, 28.
19. Herman, C.: Arch. Pediat., 1915, xxxii, 583.
20. Mauriac, P., and Philip, P.: Ann. de méd. et chir inf., 1914, xviii, 475.
21. Krever, A. R.: Russk. Vrach., abstr., Jour. Am. Med. Assn., 1914, lxiii, 2170.

Loewe and Meyer[22] report two cured cases of pneumococcus meningitis by the administration of ethylhydrocuprein. They gave 5 c.c. of a 1 per cent. solution intraspinally.

Leschke[23] states that Wolff had a recovery in an 8 months old baby with this drug.

Boland,[24] Terbutt,[25] Alan Brown,[26] Ely,[27] Hill and Packard[28] report cases of influenzal meningitis. Of the five patients reported by Hill and Packard, one survived. All the other cases terminated fatally.

Atkinson[29] reports a case of meningitis associated with an influenza-like bacillus. Besides the gram-negative bacilli, long wavy filaments and twisted spirals were observed. The finding suggests the possibility that some of the so called leptothrix forms sometimes seen in the spinal fluid from patients with meningitis, are, in reality, aberrant forms of *Bacillus influenzae*.

A singular case of meningitis in a two week old infant is reported by Garmer and Havelocque.[30] The spinal fluid showed the typhoid bacillus. The child was breast fed, and the mother gave no past history of typhoid infection.

Goebel[31] reports a proteus meningitis in a new-born child. The clinical picture was that usually seen with any form of meningitis. A pure culture of *Bacillus proteus* was obtained from the spinal and ventricular fluid. The blood serum of the patient agglutinated the organism in a 1 to 60 dilution but did not agglutinate a stock culture of *Bacillus proteus*. The child presented an odor similar to that given by the organism growing on culture media.

Rutelli[32] reports a case of streptothrix meningitis in a 6 months infant. The organism was cultivated in pure culture on Bordet-Gengou media.

A puzzling case of recurrent meningitis due to lead in a child of 5 years is reported by Thomas and Blackfan.[33] The patient was taken sick five days before admission to the hospital with characteristic symptoms. A lumbar puncture brought clear sterile fluid, cells 20-40,

22. Loewe, E., and Meyer, F.: Berl. klin. Wchnschr., 1915, lii, 1018.
23. Leschke, E.: Deutsch. med. Wchnschr., 1915, xli, 1359.
24. Boland, C. V.: Lancet, London, 1915, clxxxix, 704.
25. Terbutt, A. H.: Med. Jour. Australia, abstr., Rev. Neurol. and psychiat., 1915, xiii, 33.
26. Brown, Alan: Canad. Med. Assn. Jour., 1915, v, 1076.
27. Ely, F. A.: Jour. Iowa State Med. Soc., 1915, v, 391.
28. Hill, R. B., and Packard, R. J.: Lancet-Clinic, 1915, lxiii, 723.
29. Atkinson, E.: Med. Jour. Australia, 1914, i, 415, abstr. Rev. neurol. and psychiat., 1915, xiii, 34.
30. Garmer, M., and Havelocque, Mme.: Nourisson, 1914, ii, 211.
31. Goebel, F.: Deutsch. Arch. f. klin. Med., 1914, cxvi, 119.
32. Rutelli, G.: LaPediatria, 1915, xxii, 713.
33. Thomas, H. M., and Blackfan, K. D.: Am. Jour. Dis. Child., 1914, viii, 377.

mononuclears predominating, globulin reaction positive. Fehling's solution was reduced. The Wassermann and Von Pirquet reactions were negative. The patient was discharged well after a month. Five months later, the patient was readmitted with a similar trouble. A lead line was noticed on the gums. Examination of the red blood cells showed characteristic stippling. The source of the lead was soon explained when the child's mouth was found covered with lead paint from his crib. The patient was discharged well. Three weeks later convulsions recurred, followed by death. No necropsy was done.

Jovane[34] records what he terms "a chronic form of meningitis" which usually ends in recovery after a number of months. During the disease a tremor is noticed. It is followed by various degrees of contractures. Other than slight pleocytosis, the spinal fluid appears normal. The etiology is unknown.

The pathologic findings of a case of pachymeningitis hemorrhagica interna, undiagnosed during life, are given by Riley.[35] The clinical diagnosis was "decomposition" and internal hydrocephalus. Wilcox[36] studied the value of Macewen's sign in the diagnosis of meningeal conditions. He found the sign present in sixty-seven of seventy-one patients who had meningitis. It was also present in all of five patients with acute poliomyelitis. Macewen's sign is best determined by the stethoscope placed on the forehead just above the base of the nose. The skull is percussed directly over the parietal region, the percussing finger going from a point just over the parietal boss to that at which the stethoscope is applied.

In "a summary of four years' clinical and bacteriologic experience with meningitis in New York City," DuBois and Neal select four signs as the most important in the diagnosis of meningitis. These are stiffness of the neck, variations of regularity in rate and depth of respiration, Macewen's sign and Brudzinsky's sign.

The differential points in the diagnosis of cerebral intoxication, meningismus and meningitis, pachymeningitis and encephalitis are emphasized by Heiman.[37] The difference between intoxication and serous meningitis, he notes, is only one of degree.

The symptoms of meningismus are frequently seen after decompression operations, according to Minz.[38] These symptoms are due to an increased amount of cerebrospinal fluid. They are especially seen following operations for tumors of the posterior cranial fossa.

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34. Jovane, A.: LaPediatria, 1914, xxii, 181.
35. Riley, F. B.: Tr. Chicago Path. Soc., 1915, ix, 233.
36. Wilcox, H. B.: Arch. Pediat., 1915, xxxii, 909.
37. Heiman, H.: Arch. Pediat., 1915, xxxii, 579.
38. Minz, V. M.: Russk. Vrach., 1914, xiii, Nos. 13 and 14, abstr., Jour. Am. Med. Assn., 1914, lxiii, 616.

DuBois and Neal have never seen a case of meningitis follow one of meningismus. They believe that meningismus is a functional condition, probably of toxic origin.

Guinon[39] maintains that the term meningitis is used rather indiscriminately to cover many conditions associated with cerebral irritation, in which meningeal inflammation does not actually exist. A number of conditions so designated are cases of encephalitis. He quotes the admirable description of encephalitis by Comby and Chartier. Guinon thinks this picture should be made more flexible. Encephalitis may be mild or severe. He reports in detail two instances of encephalitis which recovered. The first, a child 4 years old, with a good family history, was taken sick after a normal convalescence from measles. One afternoon during her play the child fell, due to weakness of her extremities. Three days later she developed a train of symptoms characteristic of encephalitis. These consisted of gradually increasing stupor, inertia and apparent unconsciousness. The motor phenomena were general rigidity, contractures of the extremities, especially on the left side, exaggerated reflexes, partial athetosis and tremor. There was no Kernig's sign or any definite rigidity of the neck. The eyes were normal. Cerebrospinal fluid was normal. This period lasted for six days, and was followed by a period of aphasia lasting ten days. About the thirtieth day convalescence began and continued rapidly. In less than ten days speech returned and movements of the extremities became normal. Recovery was complete, except that there persisted a slight degree of facial asymmetry noted during laughter. The pathogenesis remains obscure. Rarely, a microorganism may be isolated, but the majority of investigators attribute the disease to a toxic origin. Guinon is unwilling to admit that the measles which the child had several weeks before the onset of this encephalitis played any rôle in the etiology of this particular case. He discusses the possibility of encephalitis being a manifestation of poliomyelitis.

MENINGEAL COMPLICATIONS OF THE CONTAGIOUS DISEASES

For persistent convulsions which occurred during the course of pertussis, which were refractory to chloral and chloroform, Fischer[40] performed ventricular aspiration. Immediate recovery followed.

Four cases of paralysis in pertussis are reported by Sorensen,[41] who discusses their probable causes. Their rapid disappearance spoke against hemorrhage as a cause, especially since the paralysis occurred during the quiescent stage of the disease. He therefore considered them of toxic origin.

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39. Guinon, L.: Arch. de méd. d. enfants, 1914, xvii, 561.
40. Fischer, L.: New York Med. Jour., 1914, c, 1054.
41. Sorensen, S. T.: Arch. f. Kinderh., 1915, lxiv, 368.

Weigert[42] records the occurrence of meningocele in an infant of 4 months as a rare complication of pertussis. After recovery the tumor slowly receded.

Wharton-Smith[43] notes that text books do not refer to acute myelitis among the sequelae of varicella, and reports such a case. Two weeks after the onset of the varicella the patient's temperature began to rise, and it was noticed that the patient's legs were drawn up. He was unable to move either of his legs or his left arm. There was also loss of sensation over these extremities. Sensation gradually returned after two weeks. His left arm was held over his head and he would scream with pain, if one attempted to pull it down or to straighten his legs. Incontinence of urine and feces was present. Fourteen months later the patient was again seen. He was able to play. There was still some spasticity of the lower extremities. The reflexes were active. There was no evidence of urinary incontinence excepting nocturnal enuresis, from which he had suffered prior to his acute illness.

The occurrence of transitory ataxia in a 7 year old boy during convalescence from measles is considered by Morichau[44] as another example of acute encephalitis, such as described by Guinon.

Rolleston[45] reports a case of extensive occlusion of the cerebral arteries following diphtheria. Two weeks after the onset of pharyngeal diphtheria the patient, an eight year old girl, complained of pain in her left chest. As her heart was being examined, she became cyanotic and unconscious, had convulsive movements of the right arm and leg, and Cheyne-Stokes respiration. The corneal reflex was absent on the right side, but active on the left side. Paralysis of the muscles of deglutition followed. Two days later death occurred. The necropsy revealed a clot filling the basilar artery, which Rolleston remarks, from his observation of eighteen cases, is the most common lesion in diphtheritic hemiplegia.

Mollet[46] collected and studied the cases of organic hemiplegia of diphtheritic origin. It occurs once in 1,500 cases. It usually follows malignant diphtheria, occurring in the second or third week. In two-thirds of the patients the hemiplegia is right sided. The prognosis is grave, not alone because of permanent contractures which follow, but on account of the high mortality, one third of the patients succumbing to the attack.

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42. Weigert, R.: Monatsch. f. Kinderh., 1914, xiii, 139.
43. Smith, Wharton: Am. Jour. Dis. Child., 1915, x, 444.
44. Morichau, R., et al.: Soc. méd. d. Hôp., July 3, 1914, abstr., Arch. de méd. d. enfants, 1915, xviii, 615.
45. Rolleston, J. D., and Guinon, E. B.: Rev. neurol. and psychiat., 1915, xiii, 373.
46. Mollét, A.: These de Paris, abstr., Arch. de méd. d. enfants, 1915, xviii, 403.

POLIOMYELITIS

Gegenbach,[47] Whitman,[48] Amesse,[49] Andrews[50] and others discuss poliomyelitis.

Flexner[51, 52] and his co-workers studied the mode of infection in poliomyelitis. They demonstrated that the virus readily reaches the central nervous system when brought into relation with peripheral nerves. Much larger quantities are necessary to produce poliomyelitis if the virus is introduced into the blood stream. The lesions in human poliomyelitis seem to correspond with those caused by intraneural and not by intravenous inoculation. Flexner considers the respiratory tract the "infection atrium" in this disease. Flexner was able to prevent the development of poliomyelitis in monkeys by the intraspinous injection of immune monkey serum. The spread of poliomyelitis is effected by the existence of healthy carriers, such having been demonstrated in the parents of an infected child and in recovered patients. There are also cases of nonparalytic ambulant forms. This has not only been proved clinically, but by the detection of changes in the cerebrospinal fluid, by the demonstration of neutralizing principles in the blood of such patients and by the determination of the virus of poliomyelitis in the upper respiratory tract.

Fraser[53] studied ninety cases of acute epidemic poliomyelitis. The symptoms usually encountered are feverishness, drowsiness, restlessness, twitching of extremities, sweating, vomiting and anorexia, rigidity of the neck, pain and tenderness, either generalized or localized to the limb involved. Similarly, the twitching may be confined to the extremity which is later paralyzed. The paralysis may involve the extremities, singly or combined, or may be respiratory or facial. Tuberculous meningitis and specific myelitis occasionally give the same clinical picture as well as cerebrospinal fluid findings as are noted in poliomyelitis. During the acute stage treatment has proven of no avail. After the acute stage massage will do much to improve paralyses. The importance of electricity is only secondary to that of massage and passive exercises.

Abramson examined the cerebrospinal fluid of forty-three patients with acute poliomyelitis. Fifteen showed a great increase in the cell count, twenty-four showed a moderate increase, four showed no increase. The lymphocytes were in excess in all but five fluids. These

47. Gegenbach, F. P.: Colorado Med., 1915, xii, 21.
48. Whitman, R. C.: Colorado Med., 1915, xii, 20.
49. Amesse, J. W.: Colorado Med., 1915, xii, 17.
50. Andrews, L. E.: Jour. Oklahoma State Med. Assn., 1914, vii, 56.
51. Flexner, S., and Amoos, H. L.: Jour. Exper. Med., 1914, xx, 249.
52. Flexner, S.: Am. Jour. Dis. Child., 1915, ix, 353.
53. Fraser, F. R.: Am. Jour. Med. Sc., 1914, cxlviii, 1.

five showed a polymorphonuclear pleocytosis. Abramson calls attention to the importance of large endothelial cells, and cells with pyriform nuclei. When he finds the former in large numbers he very strongly considers poliomyelitis. The cell count and globulin reaction in Abramson's examinations show a parallel relationship, contrary to what has been stated by the Rockefeller Institute workers. There exists an inverse relation between the amount of globulin and the reduction of Fehling's solution.

Sawyer[54] made an epidemiologic study of poliomyelitis in northern California. He demonstrated the active virus of poliomyelitis by animal inoculation in the rectal washings from a patient fourteen days after the onset of the paralysis.

Netter[55] reports his results obtained in the treatment of acute poliomyelitis by the use of serum obtained from individuals who have had the disease. He used the serum intraspinally in doses of 5 to 13 c.c., repeating the dose daily for eight consecutive days. Early administration is necessary, "from the first to the fourth day." Of thirty-two cases treated in this manner, six were completely cured, three were practically cured, twelve were improved, three were unchanged, eight died.

Alfara and Hitce,[56] following Netter's technic, treated an acute case of poliomyelitis in an infant of 7 months. On the fourth day of its illness, the baby was completely paralyzed. On the seventh day, 2 c.c. of serum was injected intraspinally. This was obtained from two children who had previously had the disease. Marked improvement resulted.

Ager[57] reports the death of two patients with afebrile, non-paralytic polioencephalitis, who were treated by autoinoculation with cerebrospinal fluid.

CHOREA AND TIC

Strauss[58] discusses the present conception of chorea. Heredity, neuropathic taint, fright and excitement have been frequently named as causes of chorea. Though these may play a rôle as predisposing causes, the exciting cause is probably of an infectious nature. The relation of chorea to rheumatism has been noted, and it has been suggested that the two diseases are caused by the same micro-organism. While from the blood of patients with arthritis diplococci are frequently isolated, the cultural and biological work that has been done on choreics has given conflicting results. At Mt. Sinai Hospital they had not been able to

54. Sawyer, W. A.: Am. Jour. Trop. Dis. and Prev. Med., 1915, iii, 164.
55. Netter, Arnold: Bull. de l'Acad. de méd., Paris, 1915, lxxiv, 403.
56. Alfaro, G. A., and Hitce, J. M.: Semana méd., 1915, xxii, 211.
57. Ager, L. C.: Arch. Pediat., 1915, xxxii, 755.
58. Strauss, I.: Med. Rec., New York, 1915, lxxxviii, 255.

isolate organisms from the blood in chorea. Strauss thinks that the therapeutic test speaks against rheumatic arthritis and chorea being manifestations of one infection, since "In chorea one does not get the good results from salicylates as are obtained in polyarthritis."

The improvement following the use of arsenic suggests the possibility that a protozoon is the causative agent.

La Fetra reports that in two of his patients a streptococcus viridans was isolated from the blood.

Koplik believes that some organism is responsible, possibly not the streptococcus, but an organism associated with the streptococcus.

In an analysis of sixteen cases of chorea Middlemiss[59] calls attention to an underlying neurotic element, which, he thinks, has not received its due importance. In four of his series there was an undoubted history of rheumatism.

Mackenzie[60] reviews the various theories which have been given regarding chorea. He reports the detailed histories of sixty-four cases, and seems rather skeptical about any common origin for rheumatic arthritis and chorea.

Certain French observers having suggested a close relationship between chorea and syphilis; Comby[61] determined the Wassermann reaction on 39 patients with chorea. Twenty-eight were negative, four were doubtful, seven were positive. Of these thirty-seven children, twenty-four gave positive tuberculin tests. This result would certainly not be interpreted as an indication of a tuberculous basis for chorea. Neither, according to Comby, do the positive Wassermann reactions in this series indicate an association with syphilis, both results being merely coincidences.

Koplik[62] made a similar study on eleven successive cases of chorea. Eight patients gave a negative Wassermann reaction. In two patients the reaction was unsatisfactory, one was not done. If the study had been prolonged, positive Wassermann reactions might have occurred, for "a child affected with syphilis might contract chorea just as readily as another." Salvarsan has no virtues over previous remedies in the treatment of chorea.

Difficulty may be experienced in the elicitation of the reflexes in choreic patients. Swift[63] suggests that the examiner choose reflexes with long pendulums such as the knee and triceps, and that the test be preceded by instructing the child to hold still. Often a number of trials are necessary. Chorea may enforce, retard or add to the usual reflex.

59. Middlemiss, J. E.: Edinburgh Med. Jour., 1915, xv, 333.
60. Mackenzie, I.: Glasgow Med. Jour., 1915, lxxxiii, 259.
61. Comby, J.: Arch. de méd. d. enfants, 1915, xviii, 517.
62. Koplik, H.: Arch. Pediat., 1915, xxxii, 561.
63. Swift, W. B.: Albany Med. Ann., 1915, xxxvi, 425, 488.

Swift[64] notes a change in pitch and intensity during the prolonged sounding of certain vowels by patients with chorea. He has named this the voice sign. The patient is allowed to sit or stand with body relaxed. The patient is instructed to take a deep inspiration and sound for 15 to 20 seconds, the vowel *a* as in *are*. During the prolongation of this note contraction in the respiratory muscles may occur, changing the intensity of the sound.

An eosinophilia in the blood of patients with chorea is noted by Leopold.[65] He studied twenty cases, 50 per cent. of which gave an eosinophilia ranging from 4 to 16 per cent. In nine patients with recurrent chorea eosinophilia was found in six.

Acuna[66] obtained brilliant results in the treatment of chorea by the intraspinal injection of magnesium sulphate. He used a 25 per cent. solution, giving 1 c.c. of this solution for every 15 kg. weight. Exceptionally, the dose was increased to 1.25 or 1.5 c.c. per 15 kg. Improvement followed rapidly and seemed permanent. In each of the six cases reported, from one to four injections were given. In one patient, in whom 3 c.c. of the solution was used, there was a cessation of all choreic movements in forty-eight hours.

Passini[67] thinks that simple lumbar puncture is a useful therapeutic measure in chorea.

Vas[68] explains spasmus nutans in childhood as a "conditional reflex." This term was first elaborated by the physiologist, Pawlow, for the interpretation of certain physiologic phenomena, such as salivary secretion on thought of certain food. The practical bearing of this reflex to children was later studied by Krasnogorski and Czerny, and by Ibrahim. Blepharospasm following conjunctivitis and the holding breath spells seen in older children who have had tetany during infancy are examples of processes explained by this reflex.

Raudnitz had previously tried to show that the chief factor in the production of spasmus nutans was the dark dwelling house. When the child was put to sleep, its constantly repeated efforts to turn its head to a light area in the room produces the condition. Nystagmus occasionally followed, which seemed analagous to the nystagmus which developes in cave dwellers.

Such conditions, resulting from abnormal innervation, need not necessarily follow habitation in a dark room, according to Vas. They may also follow repeated efforts on the child's part to turn its head for hearing a certain sound, such as a clock, or to see a certain object, as

64. Swift, W. B.: Am. Jour. Dis. Child., 1914, viii, 279; 1915, ix, 132.
65. Leopold, S. S.: New York Med. Jour., 1914, c, 225.
66. Acuna, M.: Semana méd., 1914, xxi, 929.
67. Passini, F.: Wien. klin. Wchnschr., 1914, xxvii, 1363.
68. Vas, J.: Jahrb. f. Kinderh., 1915, lxxxi, 123.

a mirror. With repetition of the strain which the muscles of the neck undergo, abnormal innervations are produced, which develop into a pathologic conditional reflex. The nystagmus secondarily follows either by the tiring of the eye musculature or by the attempt of the eye to produce sharper pictures on the retina, which does not receive such if the head is being moved constantly. It has been shown in the dog that such movements may produce concomitant nystagmus.

The diagnosis and treatment of habit spasm is discussed by Grossman.[69] He states that the distinction between chorea and tic is easily made. "Movements in chorea are more irregular, incoordinated, and less rapid. The movements in tic are more regular, purposive, and repeated at intervals in just the same manner." Observation of these movements aggravates them in chorea, but lessens them in tic. Tic may affect any muscle or group of muscles. Blinking the eyelids is the most commonly observed. Such a tic may be accompanied by a facial grimace. Grossman gives the patient a tonic, prescribes a proper hygiene, but more important still is the reeducation of the patient. This is accomplished by proper breathing exercises, and muscular exercises which Grossman describes in detail.

Cockayne[70] reports what he terms "the jaw-winking phenomenon," in an infant. When the patient was a month old the right eyelid "went up and down" when the baby nursed. At six months there was a slight ptosis of the right upper lid. Cockayne thinks there must have been a defect of the motor path for the movement of the upper lid, at least, of that part above the nucleus of the third nerve.

SYPHILIS

Camp[71] calls attention to the variety of manifestations exhibited in syphilitic infection of the central nervous system. Chronic encephalitis or meningo-encephalitis are the usual pathologic conditions found. He states that, "Syphilis as a cause of epilepsy is well known. A great many cases of idiopathic epilepsy are due to syphilis, and in a certain number of cases the syphilis is congenital." Mental deficiency is another of its manifestations.

Keyser[72] reports a case of syphilitic hemiplegia in a child aged 5. The symptoms disappeared under antisyphilitic treatment.

Rohde[73] gives a detailed clinical and pathologic report of a case of syphilis of the brain.

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69. Grossman, M.: New York Med. Jour., 1915, cii, 339.
70. Cockayne, E. A.: Brit. Jour. Child. Dis., 1914, xi, 352.
71. Camp, C. D.: Am. Jour. Urol., 1915, xi, 233.
72. Keyser, T. J.: Boston Med. and Surg. Jour., 1915, clxxii, 344.
73. Rohde, M.: Monatschr. f. Psychiat. u. Neurol., 1914, xxxvi, 407.

Encephalitis of syphilitic origin may produce lesions not unlike those of an ordinary encephalitis according to Péhu and Gardière.[74] They report the sudden occurrence of hemiplegia in a two year old child, who had congenital syphilis. Death occurred in five days. Anatomically and histologically, the lesions could not have been distinguished from other forms of encephalitis. Large numbers of treponemata were found. The clinical diagnosis must depend upon the existence of syphilis in the parents or the occurrence of stigmata in the patient, or, finally, the action of mercury.

Zondek[75] observed a very puzzling case of apparent cerebral syphilis, which diagnosis the necropsy disproved. The patient was a well-developed and well-nourished infant, with a slight adenopathy, a palpable spleen and a weakly positive Wassermann reaction. During its stay in the hospital vomiting occurred, which was followed by the development of paresis and contractures on the left side. Despite the mercurial treatment the vomiting persisted, convulsions set in and general condition grew worse. Two subsequent Wassermann tests gave a three plus reaction. Lumbar puncture disclosed a clear fluid, under pressure, globulin positive, polymorphonuclear and mononuclear cells equal. The eye grounds showed a double neuroretinitis with a one-sided choked disk. Several weeks later the right side became spastic, and the child had tonic-clonic spasms, beginning on the left side, ending on the right side. Lumbar puncture was repeated. Lymphocytes predominated. Diphtheria and bronchopneumonia finally caused death. A diagnosis of hydrocephalus internus luetica with probable gumma was made. Necropsy showed no signs of syphilis (Aschoff). There was an extensive softening of the right frontal lobe, thrombosis of the longitudinal and transverse sinuses, and thrombosis of both Sylvian arteries; no endarteritis; external hydrocephalus.

The positive Wassermann reactions Zondek explains by an accumulation of lipoids in the blood stream from the broken down brain tissue. The choked disk is explained by increased intracranial pressure, the lymphocytosis by meningeal irritation.

Juvenile paresis is often overlooked in children, according to Leroux and Weinzweig.[76] A number are diagnosed as chronic meningoencephalitis. The somatic signs resemble those seen in the adult, namely, arrest of physical development and nondevelopment of the sexual organs. Children do not usually show the ideas of grandeur and persecution so common in the adult. A change in character and intelligence usually occurs. The child becomes taciturn and inattentive, loses his memory, and complains of headache and insomnia. Occasionally, the

74. Péhu et Gardière: Arch. d. méd. d. enfants, 1915, xviii, 330.
75. Zondek, H.: Deutsch. med. Wchnschr., 1915, xli, 558.
76. Leroux, C., and Weinzweig, M.: Arch. de méd. d. enfants, 1915, xviii, 377.

beginning is abrupt, with epileptiform or apoplectiform attacks. Evolution is progressive without remissions. The average duration is from three to five years. The disease may be confused with idiocy, epilepsy, tumors or meningitis.

Schick,[77] Loffer,[78] Leonard,[79] Gostwyck,[80] Collett[81] and others report cases of the disease observed in children.

Barkan[82] discusses infantile and juvenile tabes, reporting twelve cases. Optic atrophy is usually the earliest symptom. Ninety-five per cent. present this symptom in childhood, in contrast to only 40 per cent. in the adult type of the disease.

The Wassermann reaction was positive in all. The patellar and Achilles reflexes were absent in 80 per cent. While in adults 80 per cent. exhibit a Romberg sign and ataxia, in children only 20 per cent. give these symptoms. Barkan says that a Romberg sign is rarely seen. Argyll Robertson pupils, and inequality of the pupils are usually present. The prognosis as regards sight is unfavorable, complete blindness being almost the rule. Mercury is of no avail.

EPILEPSY

Schlutz[83] says that a large number of infants have epilepsy. He makes some interesting observations in regard to its manifestations in childhood. The majority of cases develop it between the first and seventh years. The diagnosis of hysteria is frequently made when epilepsy is the disease present. The earlier epilepsy develops, the more unfavorable is the prognosis. Children seldom injure themselves during an epileptic attack. Very probably, these children have aura.

Turner[84] calls attention to the possible temporary remissions that occur in children at the age of 4 or 5, lasting until puberty. The treatment is very unsatisfactory.

Clarke[85] explains the pathogenesis of epilepsy on a Freudian basis. Epilepsy is essentially due to an arrest in the development of the psychosexual libido, he thinks. In this conception of epilepsy, the "fit" is explained as a libidinous outlet for the infantile unconscious, the nucleus of which is a desire on the part of the epileptic to return to a state of infancy. Close analysis of the epileptic supports this idea. The mental makeup of the epileptic resembles that of the child. They

77. Schick, B.: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh., 1914, xiii, 217.
78. Loffer, W. B.: Cleveland Med. Jour., 1914, xiii, 607.
79. Leonard, E. F.: Illinois Med. Jour., 1915, xxvii, 443.
80. Gostwyck, C. G. H.: Jour. Ment. Sc., 1915, lxi, 254.
81. Collett, A.: Jahrb. f. Kinderh., 1914, lxxix, 24.
82. Barkan, H.: California State Jour. Med., 1914, xii, 488.
83. Schlutz, F. W.: Journal-Lancet, 1914, xxxiv, 504.
84. Turner, W. A.: Brit. Med. Jour., 1914, ii, 665.
85. Clarke, L. P.: New York Med. Jour., 1915, ci, 385, 442, 515, 567, 623.

memorize easily, while their constructive imagination is absent. In their speech, handwriting and deportment, they always show a childlike nature, never developing specific character individuality. An analysis of their dreams shows a similar condition. The dominance of the parents, the large number of simple repressed child wishes, and the functional character of the dream imagery is striking. The movements in the convulsion are very analagous to certain moods commonly seen in the infant, such as "the deflection of the head to the side, the quadrangle mouth, etc." The prognosis is good in proportion to the possible development of the individual adolescent.

Shaw[86] states that the manifestations of epilepsy are due to a sudden "anemia of the cortex causing a discharge of the cortical nerve cells." This anemia is produced by sudden stasis and agglutination of the nucleoproteid coagulative elements of the blood in the cortical capillaries. The unusual tendency to agglutinate and the decreased alkalinity of the blood which is present in epilepsy makes this always possible.

Amesse[87] believes that chronic intestinal indigestion plays a great part in the production of epileptiform seizures. The obvious remedy is therefore dietary regulation.

Reed[88] has noticed that relief of constipation often cures epilepsy. He thinks that epilepsy is an infectious disease, the infecting agent being probably located in the intestinal tract and favored by mechanical constipation. Reed therefore proposed to remove the cause by performing an ileosigmoidoscopy followed by a colectomy, and reports favorable results.

Roentgenologic studies of the head, particularly of the sella turcica, in patients with epilepsy, were made by McKennan[89] and his co-workers. They found an overgrowth of the anterior and posterior clinoid processes, which are not only increased in area and length, but are folded over the pituitary gland. This bony overgrowth practically causes a local acromegaly.

Löwy[90] studied the blood during an epileptic seizure. He found, principally, a rise in the refractive index and a slight leukocytosis. Attacks of jacksonian epilepsy resulting from intracranial telangiectasis are reported by Sachs.[91] The patients were each 10 years old. One showed a vascularity, involving chiefly the dura, the other the cortex. One of these patients presented telangiectasis of the face. In similar cases telangiectasis has been reported on other parts of the body.

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86. Shaw, J. J. M.: Jour. Ment. Sc., 1914, lx, 398.
87. Amesse, J. W.: Colorado Med., 1914, xi, 424.
88. Reed, C. A. L.: Jour. Am. Med. Assn., 1915, lxiv, 1047.
89. McKennan, T. M. T., Johnson, G. C., and Henninger, C. H.: Pennsylvania Med. Jour., 1915, xviii, 429.
90. Löwy, J.: Zentralbl. f. inn. Med., 1914, xxxv, 985.
91. Sachs, E.: Am. Jour. Med. Sc., 1915, cl, 565.

The unsatisfactory results of treatment in epilepsy is indicated by the numerous measures recommended from year to year for its treatment.

Brodsky[92] thinks that the bromids are the best drugs to use. However, the physical and dietetic treatment are of primary importance. Protein food should be reduced to a minimum and salt given only sparingly. Institutional treatment is most satisfactory.

Crotalin has given poor results according to Yawger,[93] while Jenkins and Pendleton[94] conclude that the number of convulsions are increased by its use, and in direct proportion to the amount used.

Held[95] noted a symptomatologic and pathologic similarity between epilepsy and rabies. He devised a serum prepared as follows:

"Blood serum and cerebrospinal fluid is gained from epileptics and passed through animals first properly prepared with rabific virus. The resultant is again conducted through a series of animals in order to attenuate unpleasant bodies." Using this serum, Held has obtained good results in the treatment of epilepsy. He deplores the use of bromids in this disease.

Kutzinsky,[96] Dubrowski[97] and Klotz[98] report favorably the results of the treatment of epilepsy with luminal (chemically, phenylethylbarbituric acid). Klotz makes no claim for curing epilepsy, but notes that it decidedly diminishes the severity of the attacks and may affect their frequency. He uses a dose of from 0.05 gm. to 0.075 gm. in very young children, and from 0.1 gm. to 0.2 gm. in older children. This dose is given on two successive evenings, followed by two evenings of abstinence, to avoid cumulative effects. This alternation is continued.

Callosal puncture is suggested by Stieda[99] as a simple, safe and useful procedure in the treatment of epilepsy. In his experience, it was followed by at least temporary improvement. He recommends the procedure for other conditions when there is associated an increased intracranial pressure.

Many cases of epilepsy are due to reflex causes, according to Kalischer.[100] These causes may be present in the skin, bone or elsewhere. When such a cause is demonstrable, the removal of the

92. Brodsky, E. S.: Med. Rec., New York, 1915, lxxxviii, 479.
93. Yawger, N. S.: Pennsylvania Med. Jour., 1914, xvii, 964.
94. Jenkins, C. L., and Pendleton, A. S.: Jour. Am. Med. Assn., 1914, lxiii, 1749.
95. Held, W.: Chicago Med. Recorder, 1915, xxxvii, 157, 342.
96. Kutzinsky, A.: Monatsch. f. Psychiat. u. Neurol., 1914, xxvi, 174.
97. Dubrowski, W. G.: Monatschr. f. Psychiat. u. Neurol., 1914, xxvi, 248.
98. Klotz, M.: Therap. Monatsh., 1915, xxix, 129.
99. Stieda, A.: Arch. f. klin. Chir., 1914, cv, 277.
100. Kalischer, S.: Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1914, xviii, 368.

peripheral irritation by operative measures may effect a cure. In children, in whom tetany is so frequent, the difficulty consists in distinguishing the two.

Surgical treatment of epilepsy, judging from the results, is unjustifiable, according to Minz.[101]

LITTLE'S DISEASE

Spiller[102] studied the histories of four patients brought to him for spastic diplegia. Their ages ranged from 16 months to 3 years and 10 months. During infancy, these patients had all had jaundice, the duration of which varied from three days to three months. Several authors have noted in the adult a close relationship between diseases of the liver and alterations of the nerve cells of the brain. Spiller discusses this possibility in its application to Little's disease in childhood.

Throckmorton[103] reviews the various theories extant regarding this disease. He reports a case of early acquired spastic paraplegia, associated with various developmental anomalies. These were hypothyroidism, icthyosis, and undescended left testicle. The presence of these conditions may be indicative of a degenerative condition which involves also the cells of the motor cortex or their neurons. Both paternal and maternal grandparents of this patient were cousins, wherefore Throckmorton observes that "consanguinity, even remote, may be a factor in the production of an inferior type or grade of human organism."

Batten and von Wyss[104] describe the atonic form of cerebral diplegia, of which they report four cases. Hypotonia of the extremities was marked, dorsiflexion of the feet on the legs and hyperextension of the legs was noted. The muscles responded normally to the faradic and galvanic current. There was no loss of sensation. If the patient was supported by the axillae, the thigh and legs became flexed at right angles with the body. Manipulation of the extremities in this position revealed spasticity. The mentality of these patients varied, deficiency being the usual finding. Three of these children were breech births. The condition may be distinguished from rachitic hypotonia by the absence of other rachitic signs, from amyatonia of Oppenheim by the electrical reactions.

Fearnsides[105] reports a similar case.

Sharpe and Farrell[106] report striking results of cerebral spastic paralysis by subtemporal decompression. A history of difficult labor,

101. Korotnoff, N. I., and Minz, V. M.: Russk. Vrach., 1914, xiii, Nos. 13 and 14, abstr., Jour. Am. Med. Assn., 1914, lxiii, 616.
102. Spiller, W. G.: Am. Jour. Med. Sc., 1915, cxlix, 345.
103. Throckmorton, T. B.: Jour. Iowa State Med. Soc., 1915, v, 358.
104. Batten, F. E., and von Wyss, W. H.: Brit. Jour. Child. Dis., 1915, xii, 65.
105. Fearnsides, E. G.: Brit. Jour. Child. Dis., 1915, xii, 166.
106. Sharpe, W., and Farrell, B. P.: Jour. Am. Med. Assn., 1915, lxiv, 482.

and changes in the fundus, by ophthalmoscopic examination, are considered indications for operation. Sixty-five patients, selected from a total of 201, were thus treated by Sharpe and Farrell. Of these, thirty-four were diplegias, eleven were paraplegias, the remaining twenty were hemiplegias. Of these, six patients died, all within ten hours after the operation. Four of the six were under 2 years of age and "poor surgical risks." The usual pathologic findings are supracortical fibrous or cystic formation, the result of birth hemorrhages.

Resection of the posterior nerve roots is recommended by some and condemned by others in the treatment of Little's disease.

The compiled statistics gathered by Gümbel[107] are very disappointing. Schultless[108] notes that the hypertonicity may improve as a child grows older, and favors the postponement of operation. Bircher[109] recommends the operation. Blahd[110] reports favorable results, having had but one death in ten patients so treated.

HYDROCEPHALUS

Dandy and Blackfan[1] divide internal hydrocephalus into two groups, recognizable clinically by the presence of phenolsulphonephthalein in the spinal canal after interventricular introduction. The patency of the communicating foramina is thereby determined.

In a normal individual phenolsulphonephthalein appears in the spinal fluid in from one to three minutes. It was also found that the dye so introduced will appear in the urine in from ten to twelve minutes and that from 12 to 20 per cent. will be excreted in two hours. If introduced into the subarachnoid space, in the normal individual it will appear in the urine in from six to eight minutes and from 35 to 60 per cent. will be excreted in two hours.

The excretion of phenolsulphonephthalein in the urine from the ventricles of patients with internal hydrocephalus of the obstructive type is prolonged. The appearance time is also delayed. The authors further state:

"In marked contrast to the negligible ventricular absorption was the high subarachnoid absorption. The appearance time in the urine and the duration of excretion following subarachnoid injections were normal."

In the type of hydrocephalus with patent communication between the ventricles and subarachnoid space there is a rapid appearance of the dye in the spinal fluid following intraventricular injection. However, "the absorption from the subarachnoid space of these patients is greatly

107. Gümbel, T.: Berl. klin. Wchnschr., 1914, li, 1353.
108. Schultless, M. W.: Rev. méd. de la Suisse romande, 1914, xxxiv, 550.
109. Bircher, M. E.: Rev. méd. de la Suisse romande, 1914, xxxiv, 550.
110. Blahd, E. M.: Lancet-Clinic, 1915, cxiii, 300.

diminished, amounting to about 10 per cent. in two hours. There is a corresponding increase in the time of first appearance of phenolsulphonephthalein in the urine and the time required for its total excretion from the subarachnoid space. The diminished subarachnoid absorption is the factor responsible for the production of the internal hydrocephalus."

The treatment of these two distinct types of hydrocephalus is obviously different. In the obstructive type surgical measures are necessary to relieve the obstruction. "In the communicating type the internal hydrocephalus is the result of diminished absorption from the subarachnoid space. At present the rational treatment would be to draw the fluid into other tissues where there is adequate absorption."

V. Bokay[111] again urges the use of Strasburger's illumination method in the determination of ventricular hydrops. Transparence is only present where the brain substance between the vault of the skull and the wall of the hemispheres is not more than 1 cm. thick. The position of the greatest amount of fluid and the thinnest part of the brain substance may thus be determined. V. Bokay recommends frequent lumbar puncture in the communicating type of hydrocephalus. In the obstructive type ventricular puncture must be done. These procedures may be repeated for a period of several years without danger. It should not be repeated oftener than every four or six weeks, nor should more than 50 c.c. be removed at one time. He reports an instance in which fifty-one punctures were done over a period of six and one-half years, followed by improvement.

Amenta[112] and Cannata[113] performed Wassermann reactions on patients with hydrocephalus. Amenta found seven positive reactions in eleven patients. Cannata obtained ten positive reactions in nineteen patients. Sixteen of the mothers gave positive Wassermann reactions. He recommends antisyphilitic treatment.

Tyler[114] and Oertel[115] report cases of hydrocephalus.

Oden[116] thinks that a contracted pelvis in the mother may be a possible cause for hydrocephalus developing after birth.

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111. V. Bokay: Jahrb. f. Kinderh., 1915, lxxxi, 17.
112. Amenta, F.: LaPediatria, 1914, xxii, No. 8, abstr., Jour. Am. Med. Assn., 1914, lxiii, 1334.
113. Cannata, S.: LaPediatria, 1914, xxii, No. 10, abstr., Jour. Am. Med. Assn., 1914, lxiii, 1888.
114. Tyler, G. T.: Jour. S. Carolina Med. Assn., 1914, x, 682.
115. Oertel, H.: Canad. Med. Assn. Jour., 1915, v, 653.
116. Oden, R. J. E.: Jour. Am. Med. Assn., 1915, lxiv, 816.

MISCELLANEOUS

Talbot[117] reports "the energy metabolism of an infant with congenital absence of the cerebral hemispheres." The patient was a large baby, weighing more than the average for its age. It was blind and apparently deaf. A decompression operation showed the cerebral hemispheres entirely absent, replaced by cerebrospinal fluid. The patient had a very low metabolism, as shown in Table 1.

TABLE 1.—J. J. M., INFANT WITH CONGENITAL ABSENCE OF CEREBRAL HEMISPHERES; METABOLISM EXPERIMENT

Subject	Body Weight Without Clothing, Kg.	Height, Cm.	Age	Periods	Heat Produced		Pulse Rate
					Per Kg. per 24 Hrs., Cal.	Per Sq. M. Body Surface, Cal.	
J. J. M.	8.43	73½	8 mos.	2	29	574	73
R. L. (normal)..	7.58	71	8½ mos.	8	59	991	115
J. J. M.	7.45	..	9½ mos.	2	35	661	94
E. G. (normal)..	9.37	74	10 mos.	5	51	907	106

Talbot's explanation for the low figures given are that the absence of volitional areas in the brain, the muscular underdevelopment, with the excessive development of fatty and bony tissues, coupled with the lack of muscular activity, made only a small number of heat units necessary.

Strauch[118] reports a case of myatonia congenita of Oppenheim, presenting usual clinical features, "pseudo-paralysis of the muscles of the extremities and trunk with the exception of the diaphragm, and an involvement of the facial muscles." There was no response to the faradic and diminished response to the galvanic current. Skin and tendon reflexes were absent. Pathologic examination of the calf musculature was made. The muscle fibers appeared small. Areolar tissue was present in excessive amounts. Large numbers of sarcolemma nuclei and apparent karyokinetic figures indicated an effort at muscle regeneration.

Dunn[119] records three cases of myatonia congenita with complete necropsy on one. The muscles showed marked atrophy with increased areolar tissue and connective tissue. Two well-defined tissue masses were seen in the sections of muscle. One seemed to be made up of

117. Talbot, F. B.: Arch. Pediat., 1915, xxxii, 452.
118. Strauch, A.: AM. JOUR. DIS. CHILD., 1914, viii, 298; ibid., 1915, x, 16.
119. Dunn, C. H.: Boston Med. and Surg. Jour., 1914, clxxi, 191.

normal muscle fibers. The other was seen, under high power, to be composed of very small muscle fibers. Vacuolation of the large fibers was noted. Cortex, cerebellum, pons and medulla were normal. The changes in the cord were so slight that "they would have passed unnoticed in a routine examination."

Brauwer and Schippers[120] report a case of myatonia congenita with clinical and pathologic findings not unlike those recorded by others.

Mott[121] records a recovery following cerebral hemorrhage in a three year old girl. The hemorrhage was produced by a skull injury.

A case of myelitis of unknown origin is reported by Ashby.[122]

Two cases of pseudohypertrophic muscular dystrophy, occurring in two boys of one family, are reported by Shaw.[123]

Blauner[124] reports three cases of Friedrich's ataxia in one family. The first child developed the disease in its third year. Ataxia, explosive speech, characteristic carriage, and drunken gait were noted. The reflexes were present. The second child developed the disease in its fifth year. The third child developed the disease in its fourth year. All of these ended fatally.

Rothmann[125] reports a case of athetosis, with anatomical lesions in the corpus striatum, in a seven year old child.

Stamm[126] reports a case of multiple sclerosis in a boy of 12. The first symptom which occurred was blindness in one eye. Examination showed a central scotoma and a retrobulbar neuritis. The gait was spastic-ataxic. Oppenheim and Babinski reflexes were present. Clonus was positive. Later, the fundus examination showed a blurring of the temporal side of the disk. The Wassermann reaction was negative. The patient improved following the use of fibrolysin.

Griffith[127] describes the noteworthy features in a patient with acute cerebellar ataxia. The patient had a rapid recovery, one month after the onset of the disease.

Moreno[128] performed necropsies on forty newly born children. Examination of the brain disclosed a laceration of the tentorium in ten, with rupture of the falx cerebri in five. He was able to reproduce a similar condition experimentally in infant cadavers by exerting pressure on the sides of the head.

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120. Brauwer, B., and Schippers, J. C.: Psychiat. en Neurol. Blad., 1914, Nos. 4 and 5, abstr., Rev. neurol. and psychiat., 1915, xiii, 32.
121. Mott, W. W.: Jour. Am. Med. Assn., 1914, lxiii, 1028.
122. Ashby, H. T.: Brit. Jour. Child. Dis., 1915, xii, 142.
123. Shaw, F. B.: Dublin Jour. Med. Sc., 1914, cxxxviii, 115.
124. Blauner, S. A.: New York Med. Jour., 1914, c, 83.
125. Rothmann, M.: Berl. klin. Wchnschr., 1915, li, 754.
126. Stamm, C.: Arch. f. Kinderh., 1914, lxiii, 199.
127. Griffith, J. P. C.: Am. Jour. Obst., 1915, lxxii, 549.
128. Moreno, S. F. M.: Arch. mens. d'obst. et de gynéc., Paris, 1915, iv, 145.

Sharpe[129] believes that spina bifida is caused "by the pressure exerted by an excessive secretion of cerebrospinal fluid, or what is more probable, some obstruction to its normal outflow." The preponderance of this anomaly in the lumbosacral region is explained on the basis that this point is the region of latest closure. The spinal cord and skin are both epiblastic tissues. The meninges and bones are mesoblastic tissues. In the third month of fetal life the adherent cord and skin are separated by the meningeal and bony structure of the canal becoming complete. The vertebrae of the dorsal region are the first to close, those of the lumbar region the last. The choroid plexuses are formed, however, in the second month of fetal life. Assuming that these may secrete an excessive amount before a proper closure occurs, and that undue pressure at this time may prevent such a closure, the mechanism of spina bifida is explained. Sharpe performed laminectomies experimentally and covered the defect with superficial sutures only. Large areas of skull were then removed and pressure applied to the head. This increased pressure caused protrusion of the meninges through the cleft.

PARALYSES UNCLASSIFIED

Fearnsides[130] describes "a case of infantile hemiplegia affecting the left half of the body with considerable under development of the left upper extremity. Jacksonian convulsions affecting the paralyzed upper extremity, petit mal."

Wright[131] and D'Espine[132] report cases of infantile hemiplegia of obscure origin.

Erbsen[133] reports a case of bulbar paralysis of traumatic origin.

Bell's palsy occurring suddenly after fright is recorded by Synnott.[134]

Platt[135] considers birth palsy the result of a primary plexus injury. In a certain proportion of cases, however, a shoulder joint or epiphyseal lesion may be present.

An unusual form of birth palsy is recorded by Gordon.[136] The condition was bilateral, symmetrical and identical in the two forearms. Two branches of the median and ulnar nerves supplying the flexor carpi radialis and flexor carpi ulnaris were apparently involved. The wrists remained extended in all movements of the forearm and arm, which were normal.

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129. Sharpe, N.: Ann. Surg., 1915, lxi, 151.
130. Fearnsides, E. G.: Brit. Jour. Child. Dis., 1915, xii, 136.
131. Wright, H. W.: Jour. Am. Med. Assn., 1915, lxiv, 1577.
132. D'Espine, M.: Rev. méd. de la Suisse romande, 1915, xxxv, 52.
133. Erbsen, F.: Monatsch. f. Kinderh., 1914, xiii, 254.
134. Synnott, M. J.: Arch. Pediat., 1915, xxxii, 210.
135. Platt, H.: Brit. Med. Jour., 1915, i, 793.
136. Gordon, A.: Jour. Am. Med. Assn., 1914, lxiii, 2282.

Moren[137] discusses the differential diagnosis of paralysis in childhood.

BRAIN TUMOR

The unusual feature of a change in character as the primary sign of a brain tumor is presented by v. Malaisé.[138] Another patient showed the usual onset of headache and vomiting. A sarcoma was found in each instance.

An apparently complete recovery after operation for a cerebellar cyst is reported by Porter.[139]

Salvini[140] removed an encephalocystocele and studied its structure. Other than twitching of the extremities due to irritation, the child appeared well after the operation. Whether this procedure will be the cause of a subsequent ataxia remains to be seen.

MENTAL DEFICIENCY

While the Binet-Simon method is still preferred in the measurement of mental capacity in childhood, numerous psychologists and neurologists maintain that its use, alone, creates false impressions in the determination of mental development.

Groszman[141] condemns the habit of making quick examinations with the Binet scale. The determination of "exceptional development" is incomplete without a proper history, body measurements, thorough medical examination and the use of intelligence and physiopsychologic tests.

Potts[142] discusses the methods "calculated to throw light upon the capacities of mental defectives for future work." In school, the child's aptness for manual work and for arithmetic should be observed. Various tests which may be of value are Warner's hand balance or an ataxiograph, where the subject holds a needle in holes of various sizes cut in a brass plate. All contacts made by the subject touching the plate are recorded by an electric battery connection.

The dynamometer measures the grip and also the dextrality, that is, the superiority of one hand over another. The use of the form board, and the cancellation of assigned symbols in a prepared form are also useful tests.

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137. Moren, J. J.: Kentucky Med. Jour., 1915, xiii, 92.
138. V. Malaisé: München. med. Wchnschr., 1914, lxi, 1562.
139. Porter, L.: Arch. Pediat., 1915, xxxii, 727.
140. Salvini, C.: Ann. Surg., 1915, lxi, 10.
141. Groszman, M. P. E.: New York Med. Jour., 1914, c, 1071.
142. Potts, W. A.: Lancet, London, 1915, clxxxix, 124.

Yerkes and Bridges[143] have devised a new scale for measuring mental capacity. Instead of using different scales for different mental capacities, a single scale is used, containing a series of tests applicable to children between 3 and 15 years. The subject is given a score in points, each question having a definite valuation. This serves as a basis for comparison with normal scores, and also makes possible a comparative appreciation of individuals which was not available by the Binet scale.

Belem and Lazar[144] introduce an additional method of testing mentality in the schoolchild—a test of speech function, particularly its grammatical expression. A series of questions are given. These are so worded that the answer necessitates the use of the various moods and tenses, as well as the comparative constructions of adjectives and adverbs.

Krause[145] urges the necessity of parental cooperation in the examination of mental defectives.

Hickson[146] examined 100 patients with mental deficiency at Vineland. All showed the reactions of spastic paralysis, indicating some organic brain lesion. The principal features are a lack of development on the affected side, a continuous Babinski reaction, irregularities in the Babinski and Oppenheim reflexes. Impairment of the lower facial branch is frequent. "It is rare to see an inmate of an institution for feebleminded whistling," says Hickson. Contractures or hypertonicity of extremities are common. A lower blood pressure may be found on the affected side. In six necropsies done by Hickson at Vineland anomalies of other organs, such as hypoplasia of the cardiovascular system, supernumerary spleens and genito-urinary anomalies were noted.

Mendelsohn[147] reaches similar conclusions though his percentages are lower. Fifteen per cent. of his series showed evidences of infantile cerebral paralysis. In 6 per cent. of this group there is residual paralysis, function having been almost entirely restored. Paresis may be associated with epileptic convulsions or with choreiform movements and various tremors.

Dodd[148] believes that poor vision may prevent a child from receiving proper training and be productive of mental deficiency.

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143. Yerkes, R. M., and Bridges, J. W.: Boston Med. and Surg. Jour., 1914, clxxi, 857.
144. Belem, P., and Lazar, E.: Ztschr. f. Kinderh., 1914, xii, 185.
145. Krause, J. T.: Med. Rec., New York, 1914, lxxxvi, 337.
146. Hickson, W. J.: Illinois Med. Jour., 1914, xxvi, 394.
147. Mendelsohn, J. J.: Illinois Med. Jour., 1914, xxvi, 409.
148. Dodd, O.: Illinois Med. Jour., 1914, xxvi, 404.

McCready[149] makes a plea for the application of mental hygiene in early childhood. "Early infancy is not too early to begin the inculcation of orderly habits of thought and action."

The care of the mentally backward child is discussed by Kendall,[150] Neustaedter,[151] and Hebberd.[152] The latter urges that a distinction be made between the "mentally defective dependent" and the "mentally deficient delinquent."

Kehoe[153] is frankly pessimistic regarding the care of the feeble-minded. He advises their custody, segregation and sterilization. Attempts at education he considers a waste of time and money.

Corwin[154] has seen mental improvement follow the removal of tonsils and adenoids.

Findlay[155] found a positive Wassermann reaction in 59 per cent. of fifteen mentally defective children. He recommends the use of neosalvarsan.

Dendy[156] gives an enthusiastic account of Dr. Fernald's institutions at Waverly and Templeton. The keynote at these institutions is "occupation." Each individual is given work, that is pleasant and suited to his capacity. The boys first learn how to handle stones and wood, then tools. "From swinging a heavy mallet they pass on to hammering nails and using choppers and saws. No time is wasted trying to teach them to do what it is impossible for them to achieve."

Stevens[157] confirms the suggestion made by Sutherland regarding the association between syphilis and Mongolian idiocy. Stevens studied the blood and spinal fluid of these patients. Of twenty cases thus studied, he obtained 10 per cent. positive Wassermann reactions on the blood serum, 25 per cent. positive Wassermann reactions on the spinal fluid. The gold chlorid reactions showed color changes of two or more degrees, in 90 per cent. of the fluids. The globulin content of the spinal fluid was increased in 90 per cent.

Beier[158] discusses the various theories given for the causation of Mongolian idiocy. He states that an individual may present a Mongolian facial appearance and possess a normal mentality. In such individuals these Mongolian characteristics usually undergo change. The Mongolian idiot never changes in appearance. Treatment is unsatisfactory. Thyroid extract is useless.

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149. McCready, E. B.: Illinois Med. Jour., 1915, xxviii, 255.
150. Kendall, W. L.: Oklahoma State Med. Jour., 1914, vii, 63.
151. Neustaedter, M.: Am. Jour. Obst., 1915, lxxii, 520.
152. Hebberd, R. W.: Albany Med. Ann., 1915, xxxvi, 19.
153. Kehoe, H. C.: Illinois Med. Jour., 1914, xxvi, 407.
154. Corwin, A. M.: Illinois Med. Jour., 1914, xxv, 400.
155. Findlay, L.: Glasgow Med. Jour., 1914, lxxxii, 241.
156. Dendy, M.: Jour. State Med., 1914, xxii, 412.
157. Coriat, I. H.: Jour. Abnorm. Psychol., 1914, ix, 139.
158. Beier, A. L.: Wisconsin Med. Jour., 1915, xiii, 348.

Coriat[159] reports explosive laughter and hydrocephalus as new symptoms in amaurotic idiocy.

Batten[160] describes a family of five children, non-Jewish, three of whom were affected with a progressive disease leading to dementia, blindness and paralysis. One of these showed changes in the macular regions of the eyes. The children became noisy, filthy in habits, and developed a spasticity of the extremities. All three died. In two of these a necropsy was done. In one no changes were observed in a histologic study of the central nervous system. In the other there was slight atrophy, with diffuse degenerative changes affecting the ganglion cells. The Wassermann reaction on the blood and spinal fluid was negative in both patients.

PSYCHIATRY

Hysteria in childhood is explained by the same mechanism as in the adult, according to Coriat.[157] He reports two cases in children, one manifesting itself by blindness, the other by convulsive attacks. A symbolic wish fulfillment formed the basis of both as shown by dream analysis. In the one case freedom from taking care of the younger members of the family represented the wish. In the other there was a typical Œdipus complex in the process of formation, a desire on the child's part to continue its relations with its mother.

D'Espine[162] reports a case of astasia-abasia in a child 9 years old, due to hysteria. There was no evidence on examination of any organic lesion. The fundi were normal. The Wassermann reaction on the blood and spinal fluid was negative.

Strong[163] reports a case of hysterical paralysis in a child 2½ years old. During play in the physician's office, the condition entirely disappeared.

Stern[164] applies Freud's teachings to the explanation of pavor nocturnus.

Anxiety neurosis is discussed by Katz.[165] He reports five cases in girls ranging from 6 to 10 years. There was no past history of illness. The children became pale and weak, seemed tired and melancholic, and looked sick. There was loss of appetite. During play they would pause and either sit still dreaming, or would get up and run back and forth. After five or ten minutes they would resume their play. In two cases the girls seemed to have been frightened by details of war. In the other three the same story was elicited on subsequent interroga-

159. Coriat, I. H.: Boston Med. and Surg. Jour., 1915, clxxiii, 20.
160. Batten, F. E.: Quart. Jour. Med., 1914, vii, 444.
161. D'Espine, M.: Rev. méd. de la Suisse romande, 1914, xxxiv, 379.
162. Strong, M.: West. Med. Rev., 1915, xx, 28.
163. Stern, A.: New York Med. Jour., 1915, ci, 951.
164. Katz, O.: Berl. klin. Wchnschr., 1914, li, 1835.

tion. Katz states that in children the cause of an anxiety neurosis is easier to ascertain than in the adult. Four of these patients had nervous parents, one was the child of a severe neurotic, a mother who had hallucinations.

Farnell[166] and Stier[167] discuss the psychopathic child.

Cordes[168] notes the rarity of psychoses in children and reports four cases.

Drysdale[169] reports a case of juvenile psychosis in a boy of 11 years. Psychopathic antecedents seems to be the strongest factor in the etiology of this condition. Anything which produces a mental or physical strain may be an exciting cause.

Rhein[170] reviews the literature on insanity in children and records several cases. The manic-depressive form is the most common variety seen.

Terman[171] reviews the recent literature on juvenile suicides. In France 150 suicides a year is the record for those under sixteen years. In all other countries the situation seems to be growing worse. An analysis of the causes shows the school to be the greatest factor. Terman pleads for a "pedagogy founded equally on psychology, physiology and neurology."

In addition to the references given in the footnotes, the following will be found of interest:

Hermann, C.: Arch. Pediat., 1915, xxxii, 902.
Hume, W. E.: Rev. Neurol. and Psychiat., 1914, xii, 281.
Stevens, H. C.: Jour. Am. Med. Assn., 1915, lxiv, 1636.
Stoos, M.: Rev. méd. de la Suisse romande, 1914, xxxiv, 614.
Wolfsohn, J. M.: Arch. Int. Med., 1915, xvi, 257.

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165. Farnell, F. J.: Arch. Pediat., 1914, xxxi, 684.
166. Stier, E.: Deutsch. med. Wchnschr., 1916, xli, 794.
167. Cordes, F.: Kinder Arzt, 1915, xxvi, 81.
168. Drysdale, H. H.: Jour. Am. Med. Assn., 1914, lxiii, 1283.
169. Rhein, J. H. W.: Am. Jour. Insan., 1915, lxxi, 471.
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